CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
206316

NAME OF APPLICANT/NDA HOLDER
Daiichi Sankyo, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SAVAYSA

ACTIVE INGREDIENT(S)	STRENGTH(S)
edoxaban tosylate	15 mg, 30 mg and 60 mg

DOSAGE FORM
tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7,365,205	April 29, 2008	June 12, 2023

d. Name of Patent Owner	Address *(of Patent Owner)*	
Daiichi Sankyo Company, Limited	3-5-1, Nihonbashi Honcho	
	City/State: Chuo-ku, Tokyo	
	ZIP Code: 103-8426, Japan	FAX Number *(if available)*: +81-3-6679-6141
	Telephone Number: +81-3-3492-3131	E-Mail Address *(if available)*: ipadmin@daiichisankyo.co.jp

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	2 Hilton Court	
	City/State: Parsippany, New Jersey	
	ZIP Code: 07054	FAX Number *(if available)*: 973-944-2808
Arthur Mann	Telephone Number: 973-944-2600	E-Mail Address *(if available)*: amann@dsi.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Publishing Services (301) 443-6740 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Arthur Mann	11/18/13

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Arthur Mann	
Address Daiichi Sankyo, Inc. 2 Hilton Court	City/State Parsippany, New Jersey
ZIP Code 07054	Telephone Number 973-944-2600
FAX Number *(if available)* 973-944-2808	E-Mail Address *(if available)* amann@dsi.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Identify the precise words of the approved labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 206316 SUPPL # n/a HFD # 110

Trade Name: SAVAYSA

Generic Name: edoxaban tosylate

Applicant Name: Daiichi Sankyo

Approval Date: 8 January 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

n/a

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

n/a

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

==========

Name of person completing form: Alison Blaus, RAC
Title: Senior Regulatory Project Manager
Date: 7 January 2015

Name of Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director of the Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ALISON L BLAUS
01/07/2015

NORMAN L STOCKBRIDGE
01/07/2015

EXCLUSIVITY SUMMARY

NDA # 206316/ORG-2 SUPPL # HFD # 161

Trade Name SAVAYSA™

Generic Name edoxaban

Applicant Name Daiichi Sankyo, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not

essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 6:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigational #1 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigational #1 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigational #1 YES☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigational #1 YES☐ NO ☐
Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Janet G. Higgins
Title: Regulatory Health Project Manager
Date: 10/22/2014

Name of Office/Division Director signing form: Ann T. Farrell, MD
Title: Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
12/10/2014

ANN T FARRELL
01/09/2015

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND
Please check all that apply: ☒ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

NDA#: 206316

PRODUCT PROPRIETARY NAME: SAVAYSA **ESTABLISHED/GENERIC NAME:** edoxaban

APPLICANT: Daiichi Sankyo

PREVIOUSLY APPROVED INDICATION/S:
(1) _none_
(2) _____
(3) _____

PROPOSED INDICATION/S:

(1) **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).

(2) _____
(3) _____

NDA STAMP DATE: 8 January 2014

PDUFA GOAL DATE: 8 January 2015

SUPPLEMENT TYPE: NME NDA

SUPPLEMENT NUMBER: n/a

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☒ *active ingredient(s) (includes new combination);* ☐ *indication(s);* ☐ *dosage form;* ☐ *dosing regimen; or* ☐ *route of administration?*

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ *No* ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ *No* ☒

*If Yes, PMR #*_____ *NDA #*_____

Does the division agree that this is a complete response to the PMR? Yes ☐ *No* ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***
☒ ***Pediatric Record***

1. Pediatric age group(s) to be waived: **Patients under 18 years of age**

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from adult-related conditions on the next page

   ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients <u>and</u> is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. ***(This reason is for Partial Waivers Only)***

3. *Provide justification for Waiver:*

Non-valvular atrial fibrillation (AF) is reported to be rare in the pediatric population. The prevalence of AF increases with age and, according to the literature, is rarely seen in young populations (Fuster et al., 2006[1]). Not only is AF in children very rare but when it does occur, it is either transient (e.g. arising as a result of a chest infection or surgery), develops as a complication of another uncommon cardiac problem (e.g. congenital heart disease or, in less developed countries, rheumatic heart disease) or is found in patients with a prosthetic valve. This is in contrast to etiologies in this mostly chronic condition in adults which most commonly results from hypertrophic or dilated cardiomyopathies stemming from hypertension, ischemic heart disease, diabetes, and/or valvular disease.

In addition to the rarity of AF in the pediatric population, antithrombotic therapy is used to reduce the risk of thromboembolism (particularly stroke) only in patients with AF who are considered to be at high risk of having a stroke. Anti-platelet or no therapy is deemed sufficient in patients at lower risk as assessed by a number of available validated risk scores (Fuster et al., 2006[1]). Key factors increasing the risk of thromboembolism are co-morbidity (coronary heart disease, hypertension, history of stroke and diabetes mellitus) and structural heart disease. In the absence of these, age is the major determinant of risk. Consequently, most children with AF (in the absence of structural heart disease) are likely to be at extremely low risk of thromboembolism, which would complicate the recruitment of a pediatric study in children with AF requiring antithrombotic treatment.

The rarity of atrial fibrillation and either its transient nature or association with other complex cardiac disease makes recruitment of a sizeable and statistically robust study of edoxaban impossible in children. Even if such patients could be recruited, it is unclear that there is an indication for anticoagulant therapy, given the extremely low risk of thromboembolism anticipated in most children with AF. The low risk of stroke and thromboembolism, coupled with the low prevalence of AF, makes consideration of an outcome study in the pediatric population infeasible.

For the three other previously approved antithrombotic NDAs for the same indication, Pradaxa (dabigatran – NDA 22512), XARELTO (rivaroxaban - NDA 202439), and ELIQUIS (apixaban – NDA 202155), a waiver was granted by PeRC.

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[1] Fuster, V., Ryden L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., Halperin, J. L., LE, Heuzey, J. Y., Kay, G. N., Lowe, J. E., Olsson, S. B., Prystowsky, E. N., Tamargo, J. L. & Wann, S. (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J, 27,1979-2030.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*
We agree with the sponsor's proposed language which is consistent with 21 CFR 201.57 - "Safety and effectiveness in pediatric patients have not been established".

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign Prostatic Hyperplasia
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment
Actinic Keratosis

Cancer:
Basal cell
Bladder
Breast
Cervical
Colorectal
Endometrial
Gastric
Hairy cell leukemia
Lung (small & non-small cell)
Multiple myeloma
Oropharynx (squamous cell)
Ovarian (non-germ cell)
Pancreatic
Prostate
Renal cell
Uterine

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 206316 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:HFD-161 PDUFA Goal Date: 1/8/2015 Stamp Date: 1/8/2014

Proprietary Name: SAVAYSA

Established/Generic Name: edoxaban

Dosage Form: Tablets

Applicant/Sponsor: Daiichi Sankyo

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):3
(Attach a completed Pediatric Page for each indication in current application.)

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

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

(b) (4)

** Please note that this record only pertains to ORG- 2 (b) (4)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☒ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☒ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☒	Neonate	__ wk. __ mo.	__ wk. __ mo.	☒	☐	☐	☐
☒	Other	0 yr. __ mo.	≤2 yr. __ mo.	☒	☐	☐	☐
☒	Other	2 yr. __ mo.	≤6 yr. __ mo.	☒	☐	☐	☐
☒	Other	6 yr. __ mo.	≤12 yr. _ mo.	☒	☐	☐	☐
☒	Other	12 yr. __ mo.	≤18 yr. _mo.	☒	☐	☐	☐
☒	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☒	☐	☐	☐
	Date studies are due (mm/dd/yy): 06/2022						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

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Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

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Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
05/02/2014

DEBARMENT CERTIFICATION

Daiichi Sankyo, Inc. 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.

Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs

November 25 2013
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206316 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: SAVAYSA Established/Proper Name: edoxaban tosylate Dosage Form: 15, 30, and 60 mg Tablets		Applicant: Daiichi Sankyo Agent for Applicant (if applicable): n/a
RPM: Alison Blaus, RAC		Division: Cardiovascular & Renal Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 8 January 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other: Public Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Included – 8Jan15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	16Mar14 14Mar14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 13Jan15 DMEPA: ☐ None 15Oct14 DMPP/PLT (DRISK): ☐ None 2Jan15 OPDP: ☐ None 2Jan15 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	7Mar14 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7 May 2014 If PeRC review not necessary, explain: n/a	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg - 28Feb12 (minutes dated 16Mar12
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg - 13Aug08 (minutes dated 24Sep08
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A - 24Jun14 (minutes dated 24Jul14
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A - 8Oct14 (minutes dated 7Nov14)
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Topline Meeting (10Sep13 – minutes dated 4Oct13)
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	30 October 2014
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 8Jan15
Division Director Summary Review *(indicate date for each review)*	☐ None 23Dec14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 9Dec14
PMR/PMC Development Templates *(indicate total number)*	☐ None 18Dec14 (PMC – Dissolution) and 5Jan15 (PMRs for Pediatric Studies – DHP)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	14Feb14, 25Sep14 (Liver Consult), 10Oct14, and 12Dec14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review – 10Oct14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	None None ☐ None 9Dec14 and 6Jan15
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 28Oct14
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 10Mar14 and 22Sep14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 19Dec14
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 19Feb14 and 30Sep14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 17Nov14
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 7Nov14
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12 Aug14 & 19Aug14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 8Jul14
❖ ECAC/CAC report/memo of meeting	☐ None 12Jun14 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review 7Oct14
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 24Feb14 and 28Feb14
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 8Sep14 and 15Dec14
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 27Feb14 and 3Apr14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharm (9Sep14)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8Sep14
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 15Dec14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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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/

ALISON L BLAUS
01/12/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206316/ORG-2	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: SAVAYSA™ Established/Proper Name: edoxaban tosylate Dosage Form: Tablets		Applicant: Daiichi Sankyo, Inc.
RPM: Janet G. Higgins		Division: Division of Hematology Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 8. 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): NME (Type 1)
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	n/a
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 1/8/2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 1/8/2015
• Original applicant-proposed labeling	☒ Included **1/8/2014**
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 1/8/2015
• Original applicant-proposed labeling	☒ Included **1/8/2014**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 12/5/2014
❖ Proprietary Name • Acceptability/non-acceptability letter(s) • Review(s)	Proprietary Name conditionally Acceptable letter ***3/16/2014*** Review ***3/14/2014***
❖ Labeling reviews *(indicate dates of reviews)*	DMPP/PLT (DRISK): 1/2/2015 OPDP: 1/2/2015 DMEPA: 12/15/2014; 10/15/2014 RPM3/19/2014 SEALD: ☒ None CSS: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review 3/11/2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 1/9/2015
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC May 7, 2014 If PeRC review not necessary, explain: n/a	Pediatric Page 5/2/2014
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	12/15/2014;11/20/2014; 11/19/2014;10/24/2014; 10/23/2014; 9/29/2014; 8/26/2014; 7/21/2014;7/2/2014; 6/26/2014; 6/18/2014; 6/17/2014; 6/2/2014;5/20/2014; 5/2/2014; 4/30/2014; 4/16/2014; 4/10/2014; 4/1/2014; 3/21/2014; 3/21/2014; 3/18/2014; 3/7/2014; 2/11/2014; 2/10/2014; 2/7/2014; 1/29/2014; 1/22/2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	5/20/2014; 5/5/2014; 5/2/2014
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	9/18/ 2013; 5/13/2011
• EOP2 meeting *(indicate date of mtg)*	4/29/2009; 11/6/2008
• Mid-cycle Communication *(indicate date of mtg)*	6/24/2014
• Late-cycle Meeting *(indicate date of mtg)*	10/8/2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	1/8/2015
Division Director Summary Review *(indicate date for each review)*	1/8/2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	12/24/2014
PMR/PMC Development Templates *(indicate total number)*	1/5/2014 (2 Templates); 12/18/2014 (PMC templates)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	**co-signed primary review 9/8/2014**
• Clinical review(s) *(indicate date for each review)*	Review: 9/8/2014 Filing: 2/19/2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**Please see clinical review: Financial disclosure review is located on page 16 of the clinical review.**

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	9/25/2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Risk Mgmt Review: 9/17/2014
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Letters : 10/8/2014; 9/30/2014(5) Review: 10/1/2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	**1/7/2015**
Statistical Team Leader Review(s) *(indicate date for each review)*	**1/7/2015**
Statistical Review(s) *(indicate date for each review)*	Review: 9/9/2014 Filing: 2/18/2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	**co-signed primary review: 12/19/2014; 10/31/2014; 9/30/2014**
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	**co-signed primary review: 12/19/2014; 10/31/2014; 9/30/2014**
Clinical Pharmacology review(s) *(indicate date for each review)*	Review: 12/19/2014; 10/31/2014; 9/30/2014 Filing: 2/19/2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	**co-signed primary review 8/19/2014 ; 8/12/2014**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Review: 8/19/2014; 8/12/2014 Filing: 1/24/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	6/12/2014
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	10/7/2014
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	**co-signed primary review 9/9/2014; 9/8/2014**
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Review: 9/9/2014; 9/8/2014; 8/22/2014 Filing: 2/24/2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	Review: 4/3/2014 Filing: 2/27/2014 n/a
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	GMP Establishment Review 3/5/2014
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Chem Review dated 9/8/2014 Under Section 2
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 11/14/2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	n/a
❖ NDAs: Methods Validation *(check box only, do not include documents)* ❖	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
•	
•	
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

JANET G HIGGINS
01/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

MEETING MINUTES

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) dated January 8, 2014, received January 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA™ (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to the telecon between representatives of your firm and the FDA on December 29, 2014. The purpose of the meeting was to discuss the DHP edits to the Edoxaban labeling.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Safety Regulatory Project Manager
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Type: Type A
Meeting Category: General

Meeting Date and Time: December 29, 2014, 3:00 PM
Meeting Location: White Oak Campus, Building 22, room 2201

Application Number: NDA 206316
Product Name: SAVAYSA™ (edoxaban tosylate) 15, 30, and 60 mg Tablets
Indication: Treatment of deep vein thrombosis and pulmonary embolism
Sponsor/Applicant Name: Daiichi-Sankyo, Inc.

Meeting Chair: Kathy Robie Suh, MD, PHD, Medical Team Leader, DHP

Meeting Recorder: Diane Leaman, SRPM

FDA ATTENDEES (Division of Hematology Products/Office of Hematology Oncology Products)
Ann Farrell, MD, Division Director
Kathy Robie Suh, MD, PHD, Medical Team Leader, DHP
Lei Nie, Statistical Team Leader
Chris Sheth, Pharmacology Reviewer
Haw-Jyh (Brian) Chiu, Pharmacology reviewer
Amy Baird, Chief, Project Management Staff
Diane Leaman, Safety Regulatory Project Manager
Bahru Habtemariam Clinical Pharmacology Team Leader
Shwu-Luan Lee, Pharmacology Reviewer

SPONSOR ATTENDEES (List of DSPD)

Kim Stranick, Vice President Regulatory Affairs
Doreen Morgan, Executive Director Regulatory Affairs
Glenn Gormley, Senior Executive Officer and Global Head R&D
Mahmoud Ghazzi, Executive Vice President, Global Head Development
Michele Mercuri, Senior Vice President, Clinical Development
Michael Grosso, Executive Director Clinical Development
John Kappelhof, Executive Director Global Project Management & Leadership
Ken Truitt, Vice President Translational Medicine and Clinical Pharmacology

John Castellana, Vice President Biostatistics and Data Operations
Youngsook Choi, Senior Director Clinical Safety and Pharmacovigilance
Diane Benezra-Kushner, Senior Director Labeling Regulatory Affairs

1.0 BACKGROUND

The purpose of this teleconference meeting is to discuss the DHP indications for this NDA. The product being discussed is SAVAYSA™ (edoxaban tosylate) 15, 30, and 60 mg Tablets. This is an anticoagulant. During review of this application, DHP requested a telecon with Daiichi to discuss the labeling. The two parties expect to further the discussion of the labeling.

2. DISCUSSION

2.1. Section 1, INDICATIONS and USAGE

Discussion:

DHP noted that the additional language proposed by the Applicant is consistent with a (b) (4) This will preclude having language in the labeling that proposes (b) (4).

The Applicant agreed that they did not (b) (4)

2.2. Section 2 DOSING and ADMINISTRATION: Treatment of DVT and PE (b) (4) : Treatment of DVT and PE: (b) (4) discuss dose adjustments for use with PgP inhibitors and/or body weight < 60kg.

Discussion:

The Applicant noted that in the summary of drug interaction study results figure 12.1, the Division of Cardiovascular and Renal Products (DCRP) wants to have the same dose or reduced dose depicted for PgP inducers (from modeling data). (b) (4) DHP prefers to present data from clinical trials, when available.

DHP noted that, in the Hokusai VTE study, the PgP inhibitor alone group was small; the number of patients who were dose-reduced because of low weight was the largest. The Applicant will send the number of patients who were dosed-reduced because of low weight and the number of patients who were dose reduced because of Creatinine clearance as a follow up.

The Applicant referenced the single dose regimen in table 6.2 of the labeling and noted that there was no 30 mg dosing in the Hokusai trial as a treatment arm, only dose-reduction. DHP noted that a practitioner who needed criteria for dose-reduction would benefit having a description of patients who received the 30 mg dose. Daiichi said there is no difference in exposure between 60 mg and 30 mg-reduced patients, but Daiichi will confirm that.

2.3 Section 6.1 Adverse Reactions Hokusai-Safety (bleeding) page 11: Hokusai VTE study

- **Clarification to FDA why DSPD considers this exposure data for Hokusai relevant**
- **Clarification to incorrect reference to CRNM bleeding in this section and our proposal to correct**
-

Discussion:

DHP noted that in the clinically relevant bleeding section, the Applicant replaced the secondary composite endpoint with the primary endpoint. The primary endpoint was clinically relevant bleeding. In the sentence that reads "The primary safety endpoint was clinically relevant bleeding, defined as the composite of major and (b) (4) clinically relevant non-major (CRNM) bleeding that occurred during or within three d s of stopping study treatment" the word (b) (4) should be deleted so that the sentence reads "The primary safety endpoint was clinically relevant bleeding, defined as the composite of major or clinically relevant non-major (CRNM) bleeding that occurred during or within three days of stopping study treatment." The Applicant agreed.

2.4 Section 12 Figure 12.1 Summary of Drug interactions study results

- **Clarification on removal of Cmax from the figure – conflicting comments from DHP and DCRP**

Discussion:

There is confusion (b) (4) in Figure 12.1 (only 60 mg single dose results are shown in the figure). DCRP proposes to not include dose reduction in the table. The Applicant and DHP noted that there was 60 mg (b) (4) dose for renally-impaired patients.

DHP proposed the Applicant explain the dosing for the two indications separately in the Dosing and Administration section of the labeling (atrial fibrillation and VTE treatment). The Applicant agreed to DHP proposal.

2.5 Section 14.2 Clinical Studies Hokusai page 25: Treatment of DVT and PE:

- **Baseline description in this section**
- (b) (4) **for Primary endpoint of the trial**

Discussion:

DHP noted that there was no previous agreement for the 1.5 non inferiority margin and it is (b) (4) with limited information.

DHP's goal is to do the best for the consumer. DHP suggested the Applicant give their best case and discuss why DHP should [redacted] (b) (4) and DHP will take it to the Statistical hierarchy. DHP will review and get back to the Applicant.

In the Section 14.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism in patients who have been treated with a parenteral anticoagulant for 5 to 10 days, in the third paragraph that begins "A total of 8292 patients . . ." in the sixth sentence that begins "Overall 9.4% had a history.." the Applicant added back "and 17.3% of the patients had an age ≥ 75 years and/or a body weight ≤ 50 kg, and/or a CrCL <50 mL/min. [redacted] (b) (4) DHP requested this be deleted because the description of the composite is not helpful and is ambiguous for characterizing the study populations. The wording looks like a claim, not a mere description of baseline characteristics. The two arms do not need to be separately described. DHP suggests the total percent of patients with [redacted] (b) (4) in the study could be given.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Regarding Section 13.2, DHP is still reviewing the labeling submitted by the Applicant. DHP will send the Applicant an email concerning this section, if needed.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide data regarding dose reduction and body weight and creatine clearance	Daiichi	December 30, 2014
Provide their best argument for [redacted] (b) (4) in labeling Section 14.2	Daiichi	January 2, 2015

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments to this meeting. The Applicant submitted draft labeling on December 29, 2014 to NDA 206316. That labeling was referenced in this telecon.

Meeting Addendum:
Daiichi submitted the requested information regarding dosing on December 30, 2014.

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

/s/

KATHY M ROBIE SUH
01/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1

MEETING MINUTES

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) dated 8 January 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to the meeting between representatives of your firm and the FDA on 17 November 2014. The purpose of the meeting was to discuss the 30 October 2014 advisory committee meeting (AC) and the application's next steps.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call

Alison Blaus, RAC
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
AC Meeting Slides Referenced

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Post-AC Guidance Meeting
Meeting Date and Time:	17 November 2014 from 1500 – 1600 EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 206316/Original 1
Product Name:	SAVAYSA (edoxaban tosylate) Tablets
Proposed Indication:	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
Applicant Name:	Daiichi Sankyo
Meeting Chair:	Robert Temple, MD
Meeting Recorder:	Alison Blaus, RAC

FDA ATTENDEES

* *Office of New Drugs, Office of Drug Evaluation I*

Robert Temple, MD	Deputy Director

* *Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products*

Norman Stockbridge, MD, PhD	Director
Martin Rose, MD, JD	Cross-Discipline Team Leader (CDTL) (ORIG 1)
	Tzu-Yun McDowell, PhD Clinical Reviewer (ORIG 1)
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager (ORIG 1)
Alison Blaus, RAC	Regulatory Project Manager (ORIG 1)

* *Office of Clinical Pharmacology*

Rajnikanth Madabushi, PhD	Team Leader – Clinical Pharmacology
Jeff Florian, PhD	Acting Team Leader – Pharmacometrics
Justin Earp, PhD	Pharmacometrics Reviewer

* *Office of Biostatistics*

Jim Hung, PhD	Team Leader – Statistics (ORIG 1)

DAIICHI SANKYO ATTENDEES

Glenn Gormley, MD, PhD	Senior Executive Officer and Global Head R&D
Mahmoud Ghazzi, MD, PhD	Executive Vice President, Global Head Development
Kim Stranick, PhD	Vice President, Regulatory Affairs
Michele Mercuri, MD, PhD	Senior Vice President, Clinical Development
Ken Truitt, MD	Vice President, Translational Medicine and Clinical Pharmacology
John Castellana, PhD	Vice President, Biostatistics and Data Operations
Doreen Morgan, PharmD, MS	Executive Director, Regulatory Affairs
John Kappelhof, MBA, PMP	Executive Director, Global Project Management & Leadership

1. BACKGROUND

SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets (NDA 206316) was submitted on 8 January 2014 for the following proposed indication(s): Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Original 1), Treatment of deep vein thrombosis and pulmonary embolism (Original 2) [redacted] (b) (4)

On 30 October 2014, the application (Original 1 only) was discussed at the Cardiovascular and Renal Drugs Advisory Committee (CRDAC). Multiple aspects of the application were discussed, including the finding that patients with normal renal function had worse efficacy vs. warfarin compared to those patients with mild and moderately impaired renal function vs. warfarin. We asked the committee whether they would approve the application and if so in which of the below three scenarios:

a) Approval of the 60-mg dose for patients with normal or mildly impaired renal function.
b) Approval of a dose higher than 60 mg for patients with normal renal function.
c) Approval only for patients with mild and moderate renal impairment.

The committee voted 9-1 for approval but had diverse opinions on the above options. This meeting was planned to discuss the outcome of the CRDAC and the Agency's plans for labeling. The PDUFA goal date for this application is 8 January 2015.

2. DISCUSSION

- *Advisory Committee Outcome*
  Dr. Temple opened the meeting to say that the 30 October 2014 CRDAC seemed to view the application favorably and that it should be approved for something although the opinions varied regarding for which patients it should be approved and whether patients with normal renal function should have exposure-matched doses instead of the highest tested dose (60 mg). He added that everyone who favored approval was in agreement that the labeling should discuss the findings of decreased efficacy in subjects with normal renal function. They believed this subset finding because there is evidence that the effect of edoxaban in reducing stroke is blood concentration related and edoxaban is 60% renally cleared, and blood levels were lower in the group with normal renal function all of which makes it likely that the poorer performance in the normal renal function subgroup was related to reduced exposure and not just a chance finding. All other novel anticoagulants exhibit the same pattern of decreased efficacy associated with presumably decreased exposures in subjects with normal renal function, but the overall difference was not as great as that observed with edoxaban. Dr. Temple offered two options:
    1. The finding in subjects with normal renal function could be the basis of language intended to limit the use of edoxaban to patients with only mild and moderate renal impairment, with strong language discouraging use in patients with normal renal function
    2. The decision could be made to approve a higher dose in patients with a creatinine clearance (CrCl) > 80 mL/min.

  The applicant said that they found the 9-1 vote reassuring and heard much of the same that Dr. Temple recapitulated. They added that they analyzed the CrCl quintiles and are trying to

explain the finding in the highest quintile. They observed that patients in this quintile had a very low warfarin event rate, primarily driven by data from Western Europe. In short, the applicant believes that they conducted a high quality study, managed warfarin well, and provided more data than the Agency is used to getting in these trials and they would like to work with the Agency to come to some mutually agreeable labeling.

- (b) (4)
(b) (4)

3. OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The extent of labeling needed to highlight the limitation of use in patients with well-preserved renal function was provided via email on 18 November 2014 and will be negotiated further in the weeks to follow.

Post-Meeting Note
Upon review of the Agency's proposed labeling to limit the use in patients with a CrCl > [redacted] (b) (4)

5.0 ACTION ITEMS

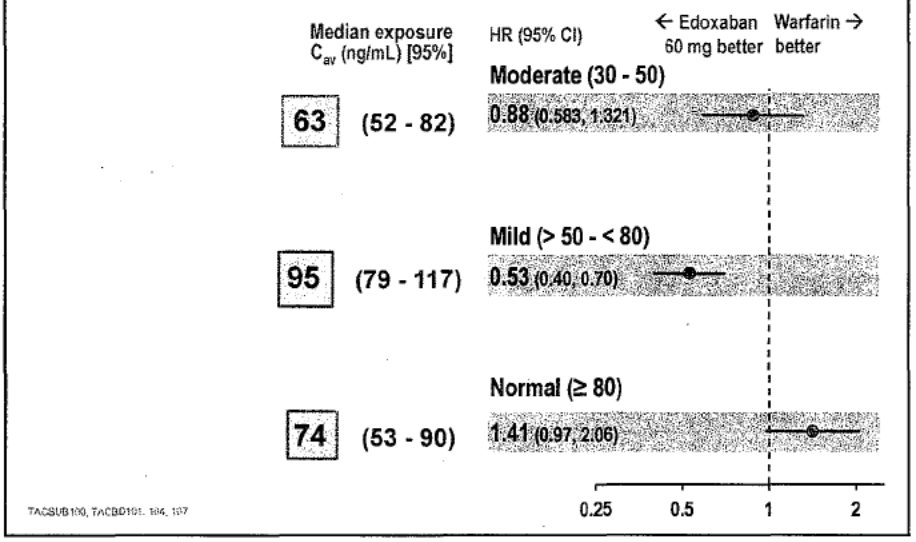
Action Item/Description	Owner	Due Date
FDA will provide the applicant with draft wording that would limit the population indicated this drug.	FDA	Done – 18Nov14
Applicant will briefly outline the safety study they plan to conduct post-action in patients administered a dose [redacted] (b) (4)	Daiichi Sankyo	ASAP

6.0 ATTACHMENTS AND HANDOUTS

The sponsor referenced a few AC slides at this meeting and they are attached to these minutes.

CI-1

Stroke or SEE by Baseline CrCL
mITT On-Treatment



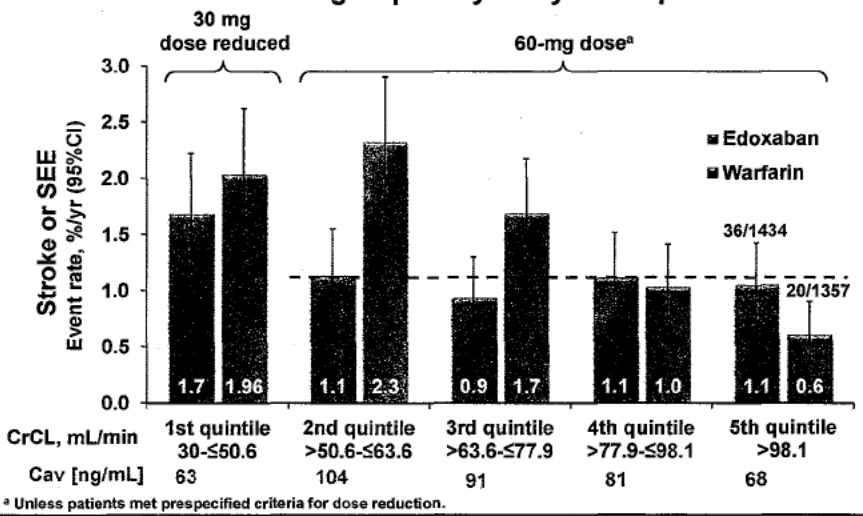
TACSUB100, TACBD101, 104, 107

Adapted from FDA briefing document, table 2, p. 18

CI-2

Stroke or SEE by CrCL Quintiles
mITT On-Treatment

Post-hoc subgroup analysis by CrCL quintiles

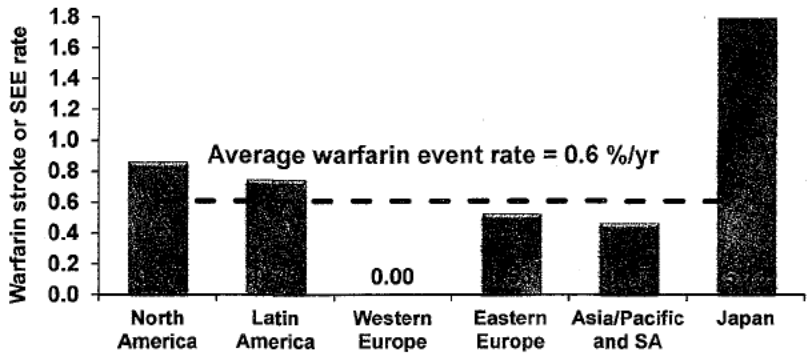


[a] Unless patients met prespecified criteria for dose reduction.

CI-3

Warfarin Stroke/SEE across Regions

Normal Renal Function Subgroup, 5th Quintile (CrCL > 98.1 mL/min)

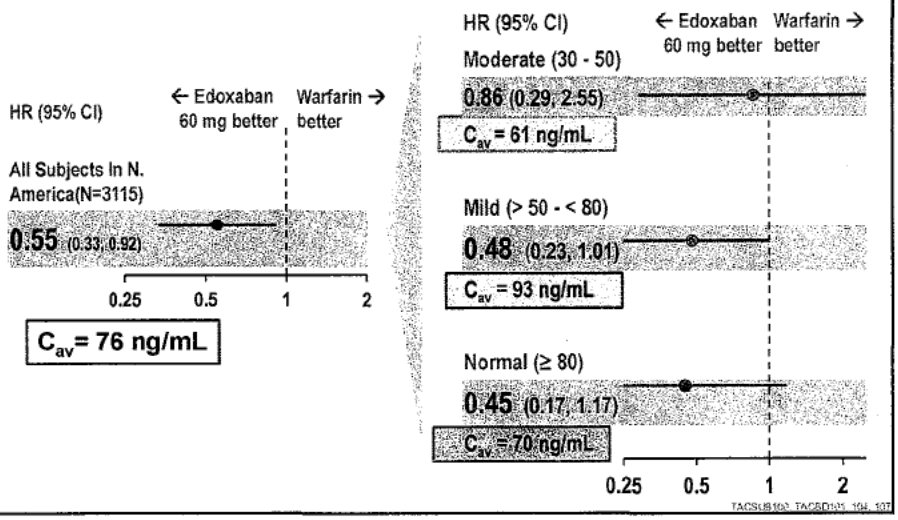


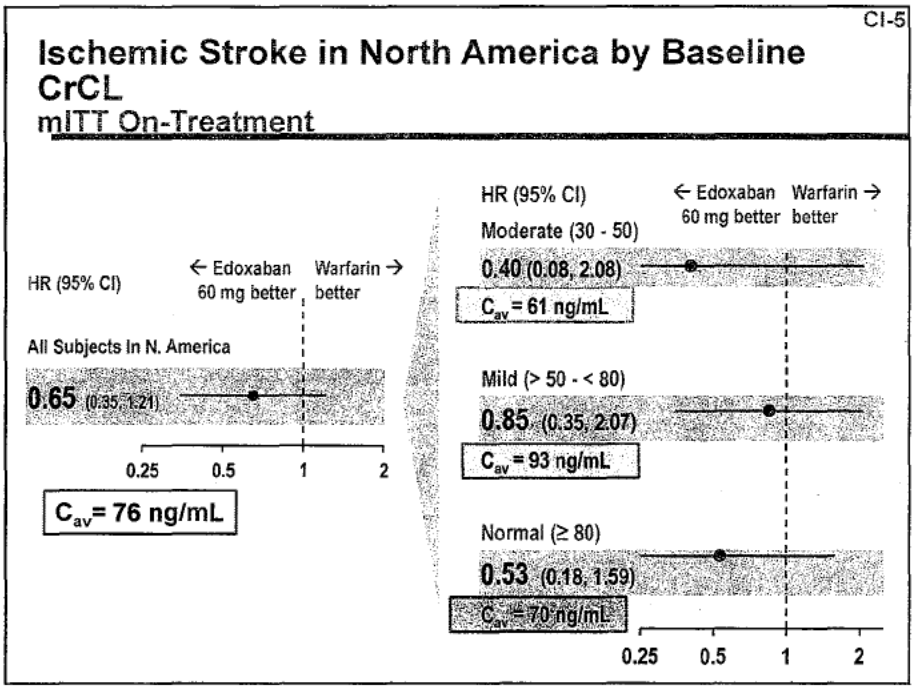
	North America	Latin America	Western Europe	Eastern Europe	Asia/Pacific and SA	Japan
n / N	7/339	2/119	0/198	8/601	1/87	2/13

CI-4

Stroke or SEE in North America by Baseline CrCL

mITT On-Treatment




CI-5
Ischemic Stroke in North America by Baseline CrCL
mITT On-Treatment
HR (95% CI)
← Edoxaban 60 mg better
Warfarin → better
All Subjects In N. America
0.65 (0.35, 1.21)
0.25
0.5
1
2
C_{av}= 76 ng/mL
HR (95% CI)
← Edoxaban 60 mg better
Warfarin → better
Moderate (30 - 50)
0.40 (0.08, 2.08)
C_{av} = 61 ng/mL
Mild (> 50 - < 80)
0.85 (0.35, 2.07)
C_{av} = 93 ng/mL
Normal (≥ 80)
0.53 (0.18, 1.59)
C_{av} = 70 ng/mL
0.25
0.5
1
2

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/s/

ALISON L BLAUS
12/17/2014

ROBERT TEMPLE
12/17/2014

From:	Higgins, Janet
To:	Morgan, Doreen
Cc:	Higgins, Janet
Subject:	PMR under PREA for NDA 206316: Edoxaban -- Please respond by 12/18/2014
Date:	Monday, December 15, 2014 2:34:39 PM

Dear Dr. Morgan:

As we continue our review of your Application, NDA 206316: Savaysa (edoxaban) tablets, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) for the venous thromboembolism (VTE) indication based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. For any new studies/trials, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol AND have already received full concurrence by the Division that the protocol is considered acceptable to address the PMR/PMC.

Upon mutual agreement on the PMR description and timeline, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Final PMR designation numbers will be assigned later.

Some things you can do to help this process:
1. Reply to our drafts ASAP, and be sure to send us, by email, your edits in a WORD document. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

a. Send us draft versions of the protocol, in WORD, by email as well as to the EDR. Again, for iterations, accept track changes sent to you that you agree with, and return the protocol to us with YOUR edits in track changes.

b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. Note also that all protocols are submitted to the IND. It is helpful to send a cross-reference letter to the NDA/BLA also.

The following are proposed:

PMR 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.

Final Protocol Submission:	03/31/2015
Study/Trial Completion:	12/1/2016
Final Report Submission:	06/30/2017

PMR Description: Perform, complete and submit the full study report for a phase 3 multicenter, randomized, active control trial of edoxaban in pediatric patients with documented venous thromboembolism in accordance with your October 31, 2013 Agreed Upon iPSP.

Final Protocol Submission:	12/14/2016
Study/Trial Completion:	12/31/2021
Final Report Submission:	06/30/2022

Please respond by **Thursday, December 18, 2014**.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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
12/15/2014

From:	Higgins, Janet
To:	Morgan, Doreen; Golikov, Gretchen (ggolikov@dsi.com)
Cc:	Higgins, Janet; Blaus, Alison
Subject:	Revised label for your NDA 206316:Edoxaban; Please respond by Monday, December 1, 2014, 1 PM EST
Date:	Thursday, November 20, 2014 10:54:54 AM
Attachments:	NDA206316_Label_DHPrev11202014jh.doc

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for edoxaban tosylate.

Please refer to the attached copy of proposed revisions to the label.

Please reply to our drafts and be sure to send me a courtesy copy via email of your edits in a WORD document that you also submit officially. Please review the changes/comments in the attached draft and do the following to the same draft.

- Use tracked changes to show YOUR edits.
- ACCEPT all of the tracked changes in our document with which you agree.
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed).
- You may provide annotation to justify your position within the PI, or, if extensive, in a separate document.

After you have made the changes, please send me the revised tracked change version before you make your official submission electronically.

Please respond by **December 1, 2014, 1pm ET** (in track change version).

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
11/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA206316

MEETING DENIED

Daiichi-Sankyo Inc.
Attention: Doreen V. Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for edoxaban tosylate.

We also refer to your November 6, 2014, correspondence requesting a type A meeting to discuss the labeling for edoxaban VTE indication. We are denying the meeting because this meeting does not meet the criteria for a type A meeting. Review of your application is ongoing and full draft labeling will be sent to you when it is substantially complete for your comment and response.

If you have any questions, call me at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JANET G HIGGINS
11/19/2014

From:	Higgins, Janet
To:	Morgan, Doreen; Golikov, Gretchen (ggolikov@dsi.com)
Cc:	Higgins, Janet
Subject:	Information Request for NDA 206316: Edoxaban ORG-2 (b) (4)
Date:	Friday, October 24, 2014 2:44:09 PM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

Please identify where you submitted the study report for the relative bioavailability /food effects study of an edoxaban pediatric formulation (specified as study 1 in the agreed-upon PSP). Please provide the location in the NDA or IND along with the study number. If you have not yet submitted the report, then please provide a status update.

Please respond by **2 PM on Thursday, October 30, 2014** via email, followed by an official submission to the NDA. Please confirm receipt.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
10/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1
NDA 206316/Original 2
(b) (4)

GENERAL ADVICE

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to the carton and container labels that were submitted as part of your initial NDA submission on January 8, 2014.

We have reviewed the referenced material and have the following comments:

A. Container Labels for 30 count, 90 count, and 500 count bottles -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, reduce the size of or delete 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, use different font colors for the proprietary name and for the strength statement to provide adequate differentiation between these strengths.[1]

[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

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).

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.

Please amend the labeling accordingly and resubmit to the NDA as soon as possible.

If you have any questions, please call the following Regulatory Project Managers:

For NDA 206316/Original 1 – Alison Blaus, RAC at (301) 796-1138
For NDA 206316/Original 2 – Janet Higgins at (240) 402-0330
[redacted] (b) (4)

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
10/22/2014

ANN T FARRELL
10/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77254

MEETING MINUTES

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for edoxaban (DU-176b).

We also refer to the meeting between representatives of your firm and the FDA on 10 September 2013. The purpose of the meeting was to discuss the results of their Phase 3 trial, ENGAGE AF-TIMI48.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call:

Alison Blaus, RAC
Regulatory Project Manager
(301) 796-1138.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor's Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Phase 3 Topline Data
Meeting Date and Time:	10 September 2013 from 930 – 1100 EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 77254
Product Name:	edoxaban (DU-176b)
Proposed Indication:	Reduce the risk of stroke and systemic embolism in patients with atrial fibrillation
Sponsor Name:	Daiichi-Sankyo Inc.
Meeting Chair:	Ellis Unger, M.D.
Meeting Recorder:	Alison Blaus, RAC

FDA ATTENDEES

* *Office of New Drugs I*	
Ellis Unger, M.D.	Director
Robert Temple, M.D.	Deputy Director
* *Office of New Drugs I, Division of Cardiovascular & Renal Products*	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Mary Ross Southworth, PharmD	Safety Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Preston Dunnmon, M.D	Clinical Reviewer
Nhi Beasley, PharmD	Clinical Reviewer
Patricia Harlow, Ph.D.	Pharmacology/Toxicology
Alison Blaus, RAC	Regulatory Health Project Manager
* *Office of Hematology and Oncology Products (OHOP)*	
George Shashaty, M.D.	Clinical Reviewer
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D.	Team Leader
Hobart Rogers, PharmD, Ph.D.	Genomics Reviewer
* *Office of Biostatistics, Division of Biometrics I*	
James Hung, Ph.D.	Director
George Kordzakhia, Ph.D.	Statistician

SPONSOR ATTENDEES

* *Daiichi-Sankyo Inc.*	
Karen Brown, Ph.D.	Executive Director, Clinical Pharmacology
Youngsook Choi, M.D.	Senior Director, Clinical Safety and Pharmacovigilance
Mahmoud Ghazzi, M.D., Ph.D.	Executive Vice President and Chief Medical Advisor, Global Development
Glenn Gormley, M.D., Ph.D.	Global Head, Research & Development and Senior Executive Officer

Sejal Emerson, PharmD	Associate Director, Regulatory Affairs
Michele Mercuri, M.D., Ph.D., FAHA	Vice President, Clinical Development
Doreen Morgan, PharmD, MS	Executive Director, Regulatory Affairs
Indravadan Patel, M.D.	Executive Director, Clinical Development
Nigel Scott, MSc, Ph.D., FRCPath	Senior Director, EU Regulatory Affairs
Minggao Shi, Ph.D.	Senior Director, Biostatistics
Kimberly Stranick, MS, Ph.D.	Vice President, Regulatory Affairs
Masafumi Yokota, DVM	Manager, New Drug Regulatory Affairs (Japan)
***** *TIMI Study Group*	
Eugene Braunwald, M.D.	ENGAGE AF – TIMI 48 study Chairman
Elliott Antman, M.D.	ENGAGE AF – TIMI 48 study Global Principal Investigator
Robert Giugliano, M.D., SM, FACC, FAHA	ENGAGE AF – TIMI 48 study Co-Principal Investigator
* *Quintiles*	
Josh Betcher, Ph.D.	Director, Statistics

1.0 BACKGROUND

Edoxaban (DU-176b) is an orally administered inhibitor of coagulation Factor Xa, being developed to reduce the risk of stroke and systemic embolic events in patients with atrial fibrillation (AF). The sponsor conducted, in conjunction for TIMI study group, one pivotal Phase 3 trial (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 - **E**ffective a**N**ticoa**G**ulation with factor x**A** next **G**Eneration in **A**trial **F**ibrillation (**ENGAGE AF-TIMI 48**)".

This meeting was scheduled to discuss the topline results from TIMI 48, additional analyses that may be requested from the Agency as a result of the discussion, as well as a few regulatory topics related to the potential dossier. The sponsor presented a number of slides during the meeting. These slides can be found as an appendix to these minutes.

2. DISCUSSION

2.1. Questions for the Agency

1. Does the Agency agree that the efficacy and safety results from ENGAGE AF – TIMI 48 study provide sufficient clinical experience to characterize the benefits and risks of Savaysa™ and to form the basis of a NDA for the identified subject population?

Discussion during the Meeting

Dr. Unger said that based on the information provided for the meeting, it appeared that the application would be reviewable. Further, he noted that ENGAGE was an adequately sized study, the follow-up appeared to be good and that the warfarin TTR was acceptable. He added that the sponsor should not only report the data by TTR but also time above therapeutic range and time below therapeutic range.

2. The results of ENGAGE AF-TIMI 48 indicate that the transition plan identified and implemented for subjects discontinuing Savaysa™ was successful and can be applied in clinical practice. The Sponsor believes that appropriate guidance can be provided in the USPI. In addition, the Sponsor believes inclusion in labeling would be sufficient and a REMS for the purpose of transition guidance is not necessary. Does the Division Agree?

   Discussion during the Meeting
   The Division, the Office of New Drugs, and Office of Surveillance and Epidemiology said that they have insufficient information at this time to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary, and if it is necessary, what the required elements would be. The Division said that the need for a REMS will be assessed during the review of the application.

3. Does the Division agree with our intent to identify optimal dosing in the NDA submission?

   Discussion during the Meeting
   Dr. Temple explained that the sponsor needs to analyze and support its view of the optimal dosing scheme in its dossier. Regarding low dose edoxaban, it is the sponsor's responsibility to identify the patient population that would have a better benefit-risk profile on the low dose, with its higher embolic event rate, than at the high dose. The Division added that the sponsor is free to analyze subgroups of the ENGAGE patient population to identify specific groups that might have a more favorable benefit-risk profile on the lower dose, but treating patients empirically with the lower dose because of a perceived greater risk of risk of bleeding would not be an acceptable rationale for approval of the lower dose. The Agency suggested that the sponsor analyze the rate of all strokes, all-cause mortality, and life-threatening bleeds in subjects on the low dose compared to the high dose. The Agency also advised the sponsor to explain why the rates of myocardial infarction/ischemic events appeared higher in the edoxaban arm compared to the warfarin arm. The sponsor agreed to provide all of the above requests for information in their initial dossier.

4. Based on the results of ENGAGE AF-TIMI 48, the Sponsor believes that the proposed NDA is appropriate for a Priority Review Designation. Does the Division concur?

   Discussion during the Meeting
   Dr. Stockbridge explained that convincing the Division that a priority review was warranted would be difficult because of the prior approvals of drugs in this class that were superior to warfarin. The sponsor stated that they would provide a rationale in their submission noting the advantage of two doses and their tested pre-specified transition plan.

5. Does the Agency concur that submitting a single eCTD to include two indications as described is acceptable?

   Discussion during the Meeting
   The Agency agreed that this was acceptable.

6. If a REMS is required for any reason, can this component of the NDA be submitted within 30 days of the initial NDA filing as allowed by PDUFA V?

   Discussion during the Meeting
   If the sponsor determines that a REMS will be necessary to ensure the benefits of the product outweighs its risks, the REMS should be included at the time of initial NDA submission.

7. Does the Agency concur with the proposed timing for a Safety Update and data lock points for this update?

   Discussion during the Meeting
   The Division agreed with the sponsor's data lock points for the 120-day safety update report.

8. Does the Agency foresee that the proposed NDA will be reviewed by the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)? If so, can the Agency comment on the timing of a CRDAC review or the earliest time point in the review cycle that the Sponsor will be notified?

   Discussion during the Meeting
   Dr. Grant noted two anti-Xa inhibitors have already been approved for reducing the risk of stroke in patients with atrial fibrillation so the Division has experience in this area. Because the results presented by Daiichi do not raise any novel efficacy or safety issues, he did not anticipate the need to discuss the application at a meeting of the CRDAC. However, the final decision about the need for an AC would be dependent on review of the data submitted in the NDA. If an AC is held, Daiichi would be notified no later than four months prior to the date of the AC.

2.2. Other Topics of Discussion

- *ENGAGE Study Design*
  - Disposition: Upon presentation of slide 3, the Division noted the low number of subjects not completing the study (~1.1%). The sponsor explained that if a subject withdrew treatment, they made every effort to keep in contact with the subject, either in person or via telephone, to obtain, at a minimum, vital status. Only subjects that completely refused all contact were deemed "withdrew consent."
  - Warfarin Naïve vs. Warfarin Experienced: The sponsor explained to the Agency that they had planned to enroll ~40% warfarin naïve patients, which was reached by the end of the trial. Dr. Temple requested that the sponsor analyze the outcome data by warfarin naïve vs. experienced.

- *Primary and Secondary Safety & Efficacy Endpoints*
  - *Analysis*: Dr. Temple asked the sponsor to include in their NDA the results comparing the high dose vs. the low dose, low dose vs. warfarin, and the high dose vs. warfarin. The sponsor was also asked to present all results using 95% CI and the 97.5% CI. The sponsor agreed to perform and submit these additional analyses.
  - *Stroke*: After presentation of slide 10, the Agency asked the sponsor to differentiate between hemorrhagic and ischemic strokes.
  - *Bleeding*: With the presentation of slide 11, Subjects with Bleeding Events, the sponsor noted that they utilized the ISTH definition for major bleed and that 60% of these events fulfilled the criterion of a 2 g/dL drop in hemoglobin. The Division

explained that they planned to review the bleeding data using ISTH, TIMI, and GUSTO definitions. The sponsor agreed to analyze bleeding using all three definitions, and committed to including all data elements for all bleeding definition sets in the NDA submission so that FDA can further analyze as needed.

- *Transition Plan*: The sponsor laid out the end of study transition plan on slide 42 and 43. They explained that patients also had their INR checked at three time points between days 4 and 14.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that that there is insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) is necessary. A decision would be made during the review of the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- In addition, we note that a chemistry pre-submission meeting was held on 17 May 2013. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no topics at the meeting that warranted further discussion.

5.0 ACTION ITEMS

There were no action items for either the sponsor or the FDA as a result of this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor presented slides at the 10Sep13 meeting. These slides are attached as an appendix to these minutes.

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/s/

ALISON L BLAUS
10/03/2013

ELLIS F UNGER
10/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1

MEETING REQUEST GRANTED

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to your 23 September 2014, correspondence requesting a meeting to discuss the 30 October 2014 advisory committee meeting (AC) and the application's next steps. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: 17 November 2014
Time: 1500 – 1600 EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Invited CDER Participants:

* *Office of New Drugs, Office of Drug Evaluation I*	
Ellis Unger,M.D.	Director
Robert Temple, M.D.	Deputy Director
* *Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products*	
Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Safety Deputy Director
Martin Rose, MD, JD	Cross-Discipline Team Leader (CDTL) (ORIG 1)
Melanie Blank, MD	Clinical Reviewer (ORIG 1)
Tzu-Yun McDowell, PhD	Clinical Reviewer (ORIG 1)
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager (ORIG 1)
Alison Blaus, RAC	Regulatory Project Manager (ORIG 1)
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, PhD	Team Leader – Clinical Pharmacology
Jeff Florian, PhD	Acting Team Leader – Pharmacometrics
Divya Menon-Andersen, PhD	Reviewer
Justin Earp, PhD	Pharmacometrics Reviewer

* *Office of Biostatistics*

Jim Hung, PhD	Team Leader – Statistics (ORIG 1)
John Lawrence, Ph.D.	Statistician (ORIG 1)

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Please e-mail me any updates to your attendees at alison.blaus@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with my name and phone number so that they can alert me to your arrival.

Please refer to the following link for visiting the White Oak Campus:
http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/ucm241748.htm

Submit a brief agenda for the meeting (three paper copies or one electronic copy to the application and an email copy to me) at least 1 week prior to the meeting. Please **do not** include questions as there is not sufficient time prior to the meeting to formulate Agency responses. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **10 November 2014**, we may cancel or reschedule the meeting.

If you have any questions, please call me at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Alison Blaus, RAC
Regulatory Project Manager
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

ALISON L BLAUS
09/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

INFORMATION REQUEST

Daiichi Sankyo Inc.
Attention: Linda Nelson, Ph.D., Director
Regulatory Affairs-CMC
399 Thornall Street, 10th floor
Edison, NJ 08837

Dear Dr. Nelson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Savaysa (edoxaban) Tablets.

We also refer to your January 8, 2014 submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by Thursday COB August 28, 2014, in order to continue our evaluation of your NDA.

1. The dissolution of your drug product using the current dissolution method does not conform to the (b) (4) Overall, we consider that the proposed dissolution model developed with the current dissolution method cannot support the proposed (b) (4) strategy for your drug product. FDA considers that to support the approval of your drug product from the Quality perspective (Biopharmaceutics and CMC) the next pathway should be followed:

A. Withdraw from your NDA submission the dissolution model and [redacted] for dissolution.

B. Implement on an interim basis the current dissolution method with an acceptance criterion of Q= [redacted]% at 30 minutes for release and on stability.

C. Modify the remaining design spaces to account for removing the dissolution model as follows:
   i. The data submitted on April 3, 2014, showed that f2 values for the comparison of some batches with the respective reference batch failed the similarly testing. [redacted]

D. Agree to the following post-marketing commitment:
   i. Within one year from NDA's action date, develop and implement a new dissolution method, which shows greater discriminating ability [redacted]
   Also, within one year set the final dissolution acceptance criterion for your drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches.
   ii. We remind you that the discriminating ability of the method is not only determined by the dissolution method conditions but also by the time point and specification value. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., ± [redacted]% change to the specification-ranges of these variables) for the most relevant manufacturing variables (e.g. [redacted]

E. If you develop a new [redacted] dissolution model with the new dissolution method, please consider the following:
   i. In order to mitigate the risk that is not addressed by the model, include [redacted] in the model. Alternatively, provide rationale with supporting data justifying the use of an alternative approach.
   ii. [redacted] construct and validate the model using 'individual mean' values of the relevant variables measured throughout the manufacturing run (e.g., 6 mean values of tablet density). [redacted] Therefore, the model should predict 'individual mean dissolution', where the inputs to the model are the 'individual means' of selected input variables measured throughout the manufacturing run.

iii. For model prediction purposes, it is recommended that the 95% one-sided lower confidence limit for the individual mean prediction be ≥ (b) (4)% for the dissolution acceptance criterion. This acceptance criterion is consistent with USP <711> Stage 1 criterion of Q+5 for each individual tablet.

F. As part of drug product's Continuous Process Verification, we recommend that you track all process variables and in-process attributes that have a potential to impact dissolution during routine production in a multivariate manner e.g. via use of MSPC (multivariate statistical process control).

Regarding other aspects of the application, we have the following information requests:

2. Provide an updated version of the CMC information in the NDA Module 3.2.S that includes the changes to the following Modules, as agreed upon in your response:

   A. SR044 (4/30/14): Section 3.2.S.2.2.1.2 Description of the Manufacturing Process for Edoxaban Tosylate; Section 3.2.S.3.1.1.4 Proof of (b) (4); Section 3.2.S.3.1.1.4 Proof of (b) (4); Section 3.2.S.4.1 Specifications; Section 3.2.S.4.5.1.1.9 Particle Size.

   B. SR057 (6/16/14): Section 3.2.S.3.2.1.4 (b) (4); Section 3.2.S.4.5.1.1.7 (b) (4); Section 3.2.S.4.4 Batch Analysis; Section 3.2.S.3.2.1.5 Potential Genotoxic Impurities; Section 3.2.S.4.5.1.1.3.3 (b) (4); Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls.

3. The change management plans for design space provided in section 3.2.P.3.4 (managing/reporting changes to design space) should be renamed as 'Protocols" and should be submitted in section 3.2.R. Regional Information. For the plan provided in Table 1.13, we have the following comments:

   A. In accordance with ICH Q8(R2), it is not necessary to report change of control space within approved design space in an annual report. Such movements can solely be managed within your own internal quality system and does not warrant any regulatory notification.
   B. Deletion of (b) (4) should be reported as CBE-30.
   C. Change of (b) (4) remain in Design Space should be reported via CBE 30.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

RAMESH K SOOD
08/26/2014
Signed for Olen Stephens

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

METHODS VALIDATION
MATERIALS RECEIVED

Daiichi Sankyo, Inc.
Attention: Doreen V. Morgan, Pharm.D., Executive Director, Regulatory Affairs
399 Thornall Street
10th floor
Edison, NJ 08837

Dear Doreen Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savaysa (edoxaban), tablets 15, 30 and 60 mg and to our July 7, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 24, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

MICHAEL L TREHY
07/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1
NDA 206316/Original 2
(b) (4)

MID-CYCLE COMMUNICATION

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on June 24, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application. A record of the teleconference is enclosed for your information.

If you have any questions, please call the following Regulatory Project Managers:

For NDA 206316/Original 1 – Alison Blaus, RAC at (301) 796-1138
For NDA 206316/Original 2 (b) (4) – Janet Higgins at (240) 402-0330

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures:
Mid-Cycle Communication
Clinical Pharmacology - Pharmacometrics Pre-read

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 24, 2014 from 0930 – 1100 EDT
Application Number: NDA 206316
Product Name: SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets
Proposed Indication:
1. Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Original 1)
2. Treatment of deep vein thrombosis and pulmonary embolism (Original 2)

(b) (4)

Applicant Name: Daiichi Sankyo
Meeting Chair: Norman Stockbridge, MD, PhD
Ann Farrell, MD
Meeting Recorder: Alison Blaus, RAC

FDA ATTENDEES

* *Office of New Drugs*, *Office of Drug Evaluation I*, *Division of Cardiovascular & Renal Products*	
Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Safety Deputy Director
Martin Rose, MD, JD	Cross-Discipline Team Leader (CDTL) (ORIG 1)
Melanie Blank, MD	Clinical Reviewer (ORIG 1)
Tzu-Yun McDowell, PhD	Clinical Reviewer (ORIG 1)
Nhi Beasley, PharmD	Clinical Reviewer
Thomas Papoian, PhD	Team Leader, Pharmacology/Toxicology
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Project Manager
Lori Wachter, RN, RAC	Safety Project Manager
* *Office of New Drugs, Office of Hematology and Oncology Products*	
Ann Farrell, MD	Director
Edvardas Kaminskas, MD	Deputy Director
Robert Kane, MD	Safety Deputy Director
Kathy Robie-Suh, MD, PhD	Cross-Discipline Team Lead r (CDTL) (ORIG 2 (b) (4)
Saleh Ayache, MD	Clinical Reviewer (ORIG 2 (b) (4)
Patricia Garvey, RPh	Senior Regulatory Project Manager
Laura Wall, MS, BSN, APHN, OCN	Regulatory Project Manager
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, PhD	Team Leader – Clinical Pharmacology
Julie Bullock, PharmD	Team Leader – Clinical Pharmacology
Sudharshan Hariharan, PhD	Acting Team Leader - Clinical Pharmacology
Divya Menon-Andersen, PhD	Reviewer
Young-Jin Moon, PhD	Reviewer
Jeff Florian, PhD	Acting Team Leader – Pharmacometrics
Justin Earp, PhD	Pharmacometrics Reviewer
Robert Schuck, PhD	Pharmacogenomics

* *Office of Biostatistics*	
Lei Nie, PhD	Team Leader – Statistics (ORIG 2 [redacted] (b) (4)
John Lawrence, Ph.D.	Statistician (ORIG 1)
Yun Wang, PhD	Statistician (ORIG 2 [redacted] (b) (4)
* *Office of New Drug Quality Assessment*	
Kasturi Srinivasachar, PhD	Branch Chief
Janice Brown, MS	Branch Chief
Akm Khairuzzaman, PhD	Reviewer
Debasis Ghosh, PhD	Reviewer
Sandra Suarez, PhD	Biopharmaceutics
* *Office of Surveillance and Epidemiology*	
Doris Auth, PharmD	DRISK Team Leader
Carolyn Yancey, MD	DRISK Reviewer
Anne Tobenkin	Pharmacovigilence
Steven Bird	OSE Regulatory Project Management
Karen Bengston	OSE Regulatory Project Management
* *Office of Medical Policy, Division of Medical Policy Initiatives*	
Sharon Mills	Patient Labeling

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou	Assessor

APPLICANT ATTENDEES

Doreen Morgan, PharmD, MS	Executive Director, Regulatory Affairs
Michael Grosso, MD	Executive Director, Clinical Development
Raymond Miller, PhD	Executive Director, Modeling and Simulation
Johannes Kappelhof	Senior Director, Project Management
Michele Mercuri, MD, PhD	Senior Vice President, Clinical Development
Hans Lanz, MD	Executive Director, Clinical Development
Linda Nelson, PhD	Director, Regulatory Affairs – CMC
George Chen, PhD	Executive Director, Regulatory Affairs – CMC
Glenn Gormley, MD, PhD	Senior Executive Officer and Global Head of R&D
Minggao Shi, PhD	Senior Director, Biostatistics
Youngsook Choi, MD	Senior Director, Clinical Safety
Kimberly Stranick, PhD	Vice President, Regulatory Affairs
Dolly Parasrampuria, PhD	Senior Director, Clinical Pharmacology
James Beech	Vice President, Quality Assurance
Indravadan Patel, MD	Executive Director, Clinical Development
John Castellana, PhD	Vice President, Biostatistics and Data Operations
Mahmoud Ghazzi, MD, PhD	Executive Vice President, Global Head of Development
Martins Adeyemo, PhD	Senior Director, Medicinal Safety
Laura Bower, MD	Director, Clinical Safety
Valentin Curt, MD	Senior Director, Clinical Development
Mike DeMarco, PharmD	Manager, Regulatory Affairs
James Jin, PhD	Senior Staff Biostatistician
Jingdong Xie, PhD	Senior Staff Biostatistician
Karen Frantz	Director, Regulatory Operations
Anil Duggal, MD	Senior Director, Clinical Development
George Zhang, PhD	Senior Staff Biostatistician
Amy Chinigo, MD	Director, Clinical Safety
Gretchen Golikov	Director, Regulatory Affairs
Fran Bessette	Senior Director, Project Management

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Chemistry, Manufacturing, and Controls (CMC)

- Dr. Suarez from Biopharmaceutics explained that she found the dissolution criterion acceptable, but that issues remained with the dissolution methods, including the (b) (4) She also noted that the specifications related to the design space (b) (4) She committed to providing these new proposed changes to the applicant by the end of the week.
- Dr. Ghosh (Drug Substance - DS) and Dr. Khairuzzaman (Drug Product - DP) have no major review or labeling issues at this stage in their review, but noted that the issues presented by Dr. Suarez (b) (4) Dr. Khairuzzaman added that these were not significant challenges. Dr. Ghosh finished the CMC portion of the meeting by asking the applicant to update Module 3 of NDA to reflect the proposed changes already submitted to the Agency via email communication. He added that his review and final decision on the changes could only be made on formal submissions.

Pharmacology & Toxicology

- Dr. Papoian explained that there were several significant findings thus far in the primary review of the pivotal pharmacology and toxicology studies, some of which may end up as labeling issues.
  1. In the chromosome aberration portion of the genotoxicity studies, the results showed increased polyploidy, an indication that edoxaban may have potential to inhibit the mitotic process. Dr. Papoian added that this item is still under review based on an evaluation of the concurrent cytotoxicity data.
  2. Findings of hemorrhage in rats, rabbits, mice, and monkeys that likely represents the pharmacologic action of the drug.
  3. In the reproductive and developmental toxicology studies, findings in rats and/or rabbits included: more post-implantation loss, fewer live fetuses, lower fetal weight, increased gall bladder and skeletal variations, and delayed avoidance response in a learning test in F1 female rats that was associated with maternal hemorrhagic toxicity.
  4. Higher mortality was seen in male rats at the high dose in the 2-year carcinogenicity studies that was associated with higher incidence and severity of centrilobular hepatocellular degeneration/necrosis. Female rats were negative at higher exposures, as were male rats that survived. No liver findings were seen in mice or monkeys.
  5. The Agency explained that the lactation section of labeling should include mention that drug was found in milk of lactating rats. However, this is already included in the proposed labeling.

6. The labeling section for pediatric use (b) (4)

Dr. Papoian concluded by saying that the Divisions (DHP and DCRP) met with the executive carcinogenicity committee (eCAC) and they concurred with Daiichi and the Divisions that the 2-year edoxaban rodent carcinogenicity studies were negative.

Clinical Pharmacology

- Ahead of the meeting, the Agency provided Daiichi with a discussion paper detailing the FDA's review of the interaction between creatinine clearance (CrCl) and safety-efficacy in patients with atrial fibrillation from the ENGAGE trial. At the meeting, Dr. Earp explained that the Agency's concerns were that reduced exposure to edoxaban was seen in patients with well-preserved renal function who received edoxaban 60 mg as well as those with moderate renal dysfunction who received 30 mg edoxaban daily resulting in excessive rates of ischemic stroke in these subgroups. The applicant acknowledged the paper that was provided and asked the Agency to confirm that they focused on the two possible endpoints of life-threatening bleed and ischemic stroke and whether it was a weighted analysis, referring to the clinical utility index they reported in their exposure response study report for the AF-ENGAGE trial. Dr. Earp stated that he looked at all strokes and SEE in addition to ischemic stroke and major bleeds in addition to life threatening bleeds, but a weighting of the events relative to each other was not used for these analyses. Instead the comparison of exposure response was made to the overall observed rate for warfarin for the specific efficacy or safety event of interest. Dr. Earp also noted that the analysis focused on ischemic stroke and life-threatening bleeds since they were important and serious events directly related to the benefits of edoxaban and its risk, respectively and thus most appropriate to evaluate benefit-risk. Dr. Earp said that he also focused on exposure matching and used the exposures observed in patients with mild renal impairment as the target. Daiichi inquired if CV mortality and all-cause mortality were also evaluated. Dr. Earp responded that they were not, at this point. Additionally, it was noted that those patients with CrCl < 30 were not evaluated in the same manner because there were so few patients that fit this demographic. The applicant acknowledged the Agency's modeling approach and agreed to provide their modeling for those patients with severe renal impairment (CrCl < 30) and is willing to discuss these analyses at a later time.

  Dr. Earp said that the same dosing issue that was seen in the atrial fibrillation trial ENGAGE was observed in the HOKASAI trial (DVT/PE trial), but he did not think that the exposure response and safety-efficacy relationship necessitate a change in the dosing recommendation at this point.

  Dr. Rose referred the applicant to a recent publication describing the novel oral anticoagulants and the theoretical concern that there may be active drug in the gut leading to an increase in gastrointestinal bleeding. If the dose is raised based on pharmacometric modeling, the Agency would like to explore this concern with them.

  Dr. Menon-Andersen concluded the clinical pharmacology portion of the meeting to note three labeling issues regarding drug-drug interaction (DDI) information and specific populations:

  1. Currently, Dr. Menon-Andersen (b) (4) . Any loss in exposure is considered not good.
  2. Dr. Menon-Andersen noted that the applicant labeled a dose adjustment for PGP inhibitors, but no adjustment needed for amiodarone. (b) (4)

[redacted]. She believes that dosing recommendation for P-gp inhibitors that may be co-administered with EDX should be uniform.

3. Lastly, Dr. Menon-Andersen said that there is not enough information on patients with moderate hepatic impairment and therefore no dose recommendations can be made in labeling. She referred the applicant to language in the Eliquis (apixaban) USPI on this topic that will be recommended for the edoxaban label.

Clinical – Atrial Fibrillation (ORIG1)

- Drs. Blank and McDowell confirmed that there is a pending OSE hepatotoxicity consult with Dr. John Senior and there are no other identified safety issues that could impact approvability at this point in the review.

Biostatistics – Atrial Fibrillation (ORIG1)

- Dr. Lawrence explained that he had some difficulty replicating the applicant's analyses, but has since been able to replicate their data noted in labeling. He concluded by saying that he did not have any significant review or labeling issues at this point in his review.

Clinical – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2) [redacted]

- Dr. Robie-Suh explained that the general concern that DHP has at this point is the rationale for claiming [redacted]. The exact indication wording is a review issue at this point, but there is a difficulty in how Daiichi [redacted]
- Dr. Ayache confirmed there are no safety issues that could impact approvability at this point.
- Dr. Robie-Suh and Dr. Nie explained that DHP does not anticipate [redacted]
- DHP commented that review is ongoing and any additional questions that arise will be communicated to the sponsor via information request.

Biostatistics – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2) [redacted]

- Dr. Wang explained that her review issue was that there is no pre-specified multiplicity adjustment to [redacted]

3.0 INFORMATION REQUESTS

At the time of the Midcycle Communication Meeting, there were a few of outstanding information requests. An abridged list of all outstanding information requests are as follows:

- Missing and incomplete adjudication packages (ORIG-1)
- Rationale for the discrepancy in the number of patients lost to follow-up cited in the clinical study report vs. the top-line minutes. (ORIG-1)

- (b) (4) method information requested dated June 17, 2014

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Safety Concerns

- There were no major safety concerns noted at this point in the review for either DHP or DCRP.

Risk Management Plan (REMS)

- Dr. Yancey explained that it is premature to reach a conclusion on whether or not edoxaban will require a REMS to ensure that the benefits outweigh the risks. A final determination will be made after the review for hepatotoxicity is completed as well as the upcoming AC in late October.

5.0 ADVISORY COMMITTEE MEETING

We are planning on holding an advisory committee (AC) to discuss the atrial fibrillation portion of this application (ORIG-1). We stated that the most likely dates for the meeting were either October 29 or 30, but after the meeting with the applicant, the AC meeting was scheduled for October 30. Based on a planned AC meeting date of October 30, the following schedule will apply:

Advisory Committee Meeting Book Due (Daiichi Sankyo): September 29, 2014
Advisory Committee Meeting Book Due (FDA): October 1, 2014
FDA Slides Due: October 28, 2014

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Setting aside the milestones associated with the advisory committee meeting, there are a few other dates to keep in mind. Those dates are as follows:

Late-Cycle Meeting (Internal): September 15, 2014
Late Cycle Meeting Briefing Book Due to Daiichi Sankyo: September 18, 2014
Late-Cycle Meeting w/Applicant: October 8, 2014

Office of Clinical Pharmacology Discussion Paper:

Summary of Exposure-Ischemic Stroke/Life-Threatening Bleeding Analyses for SPAF Indication of Edoxaban (NDA 206316)

The purpose of this paper is to facilitate discussion at the upcoming Midcycle communication meeting for the edoxaban NDA.

Summary of Dosing Considerations:

The exposure-response relationships shown below (Figure 1 and Figure 2) suggest:

1) Patients with normal renal function may benefit from an increase in dose

2) Increasing exposures in patients with normal renal function to match those in the 60 mg mild renal insufficiency group is not expected to increase the risk of life-threatening bleeds beyond that observed for warfarin in the corresponding subgroup

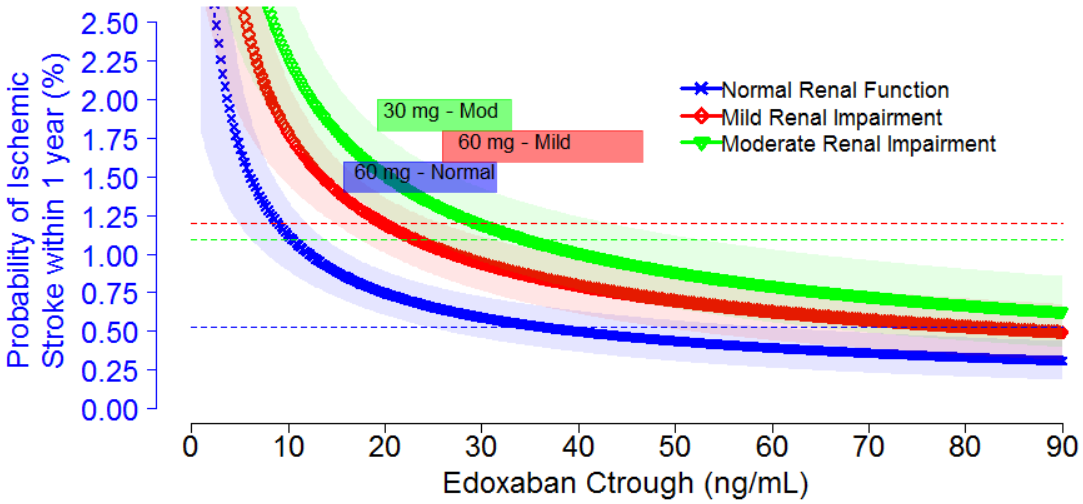
3) For patients with moderate renal insufficiency, a dose adjustment to 45 mg QD that results in exposure matching to patients with mild renal insufficiency is expected to decrease the risk for ischemic stroke and is not expected to increase the risk for life threatening bleeds greater than that observed in patients treated with warfarin

Discussion of Analyses:

Sub-group analysis of study 301 (Figure 11.3 in CSR), identified renal function as a significant predictor for reduction of stroke/SEE (interaction p = 0.0002). Of note, subjects with normal renal function (CRCL >= 80 mL/min) in the edoxaban 60 mg did not exhibit relative benefit over warfarin and numerically appears worse than warfarin (HR: 1.41, 95% CI: 0.97-2.06). Similar results were also found in the edoxaban 30 mg group. As expected, this outcome appears to be the result of lower edoxaban concentrations (Mean population PK estimated trough exposure for normal renal function at 60 mg QD is 23.6 ng/mL) compared to the mild impairment group (CRCL ≥50 – 80 mL/min) that received 60 mg (Mean exposure is 34.8 ng/mL). Consistent with this finding, the risk for major bleeding, relative to warfarin, is numerically higher in patients with mild impairment of renal function compared to those with normal renal function. Further, in patients with moderate impairment of renal function, dose reduction to 30 mg QD seems to be an over correction. Based on these observations the review team embarked on exposure-response analyses.

A multivariate Cox proportional hazards analysis identifies edoxaban trough concentration, among others, as a significant predictor of reduction in risk of ischemic stroke as well as increase in the risk of life-threatening bleeds. This analysis allows for a better understanding and optimizing of the benefit-risk across different subgroups with different edoxaban exposures. The following figures and tables provide the topline results that form the basis of the suggested dose adjustments.

Figure 1. Multivariate cox proportional hazards analysis suggests that the exposures in those with normal renal function receiving 60 mg are insufficient in reducing the risk of ischemic stroke (mITT population, on-treatment + 3 days censor) when compared to warfarin. Each symbol (with corresponding bands) represents the Cox model prediction with 95% CIs for a typical patient representing normal renal function (blue), mild (red), and moderate (green) renal impairment populations, respectively, in Study 301. Dashed lines represent the mean observed annualized event rate for warfarin in each of the corresponding renal function groups. The bars color-labeled with their corresponding group indicate the exposure range for that subgroup of patients (5th to 95th percentile).



Event rates for warfarin were calculated as 100*(n events/Total Number of individuals)/(Sum of Individual Times in days/(Total Number of Individuals*365 days/year))

Figure 2. Multivariate cox proportional hazards analysis suggests that edoxaban exposures are below the levels required to match warfarin's bleeding risk (life-threatening bleeds, mITT population, on-treatment + 3 days censor). Each symbol (with corresponding bands) represents the Cox model predictions with 95% CIs for a typical patient representing normal renal function (blue), mild (red), and moderate (green) renal impairment populations, respectively, in Study 301. Dashed lines represent the mean observed annualized event rate for warfarin in each of the corresponding renal function groups. The bars color-labeled with their corresponding group indicate the exposure range for that subgroup of patients (5th to 95th percentile).

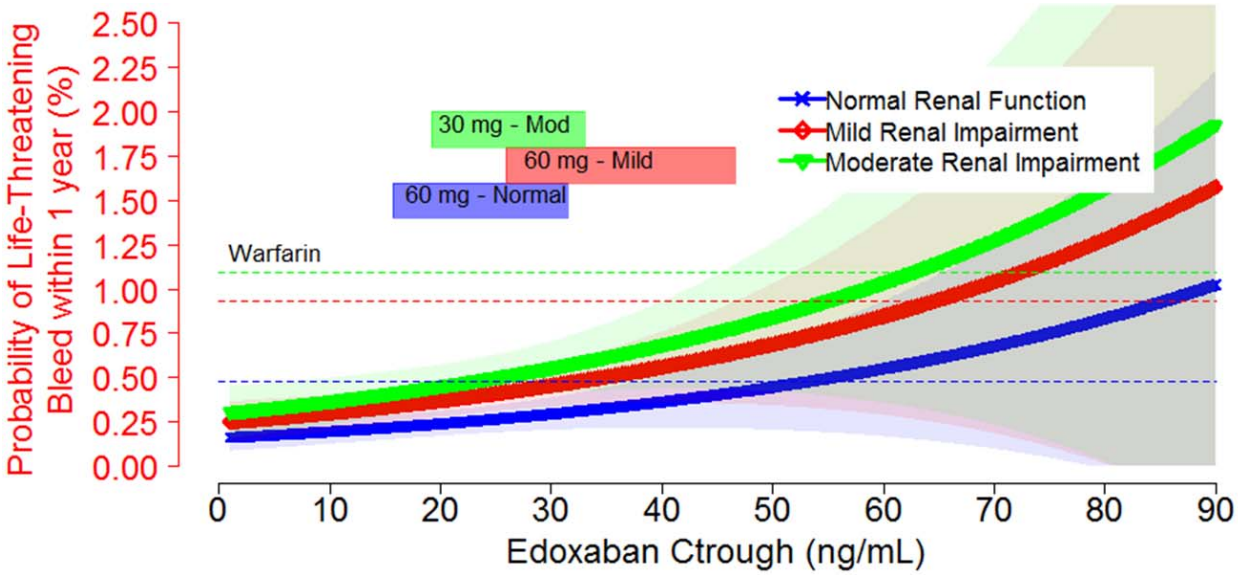


Table 1. Parameter estimates of the final ischemic stroke exposure-response model

Parameter	Estimate	Standard Error	p-value
Treatment	-1.93	0.31	6.2e-10
CrCL	-0.00824	0.00219	1.7e-4
Age	0.0125	0.00632	0.049
History of Stoke/TIA	0.8801	0.0898	0
Log(trough concentration)	-0.58868	0.10445	1.7e-8

Table 2. Parameter estimates of the final life-threatening bleed exposure-response model

Parameter	Estimate	Standard Error	p-value
Treatment	1.367	0.251	5.3e-8
Age	0.0402	0.00803	5.4e-7
History of Stoke/TIA	0.522	0.137	1.4e-4
Aspirin Use	0.424	0.138	0.011
Trough concentration	0.0209	0.0088	0.0022

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

/s/

NORMAN L STOCKBRIDGE
07/24/2014

EDVARDAS KAMINSKAS
07/24/2014

From: Agosto, Teicher
To: "lnelson@dsi.com"
Subject: NDA 206316 Information Request
Date: Monday, July 21, 2014 5:01:00 PM

Dear Dr. Nelson,

We are requesting the following additional information concerning your New Drug Application- NDA 206316. We request a prompt response to this IR request no later than COB Friday, August 1, 2014.
Please provide information for the following comments:

The change control plans for (b) (4) proposed under *Continuous Model Verification* in Section 3.2.P.5.3 should be renamed as "Protocols"; and should be submitted in section 3.2.R. *Regional Information*. For the protocols outlined in Table 1.7 (b) (4) Table 1.2 (b) (4) and Table 1.14 (b) (4)), we have the following *Information Request*:

- Change in the model type (from (b) (4) to PCR) does not belong to continuous model verification; therefore should be removed from the protocols. For this type of change, you will need to submit a PAS supplement seeking the Agency's approval prior to the implementation of the change.
- Critical changes (i.e. Level 3 changes) should be reported as a CBE-30.
- Specify the composition of the data sets and the acceptance criteria used to verify each level of change. Clarify the data sets for internal or external validations; and batch information (number of batches, batch size, manufacturing sites etc.) of the data sets.
- The examples given under "change" columns are incomplete and not sufficiently descriptive. Provide a more complete list of potential changes and describe types (or similar) of changes expected for the methods.
- To facilitate review, discuss possible circumstances that would prompt level 2 and level 3 changes.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov

P: (240) 402-3777

APPEARS THIS WAY ON ORIGINAL

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/s/

TEICHER N AGOSTO
07/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

REQUEST FOR METHODS VALIDATION MATERIALS

Daiichi Sankyo, Inc.
Attention: Doreen V. Morgan, Pharm.D.
Executive Director, Regulatory Affairs
399 Thornall Street, 10th floor
Edison, NJ 08837

Dear Doreen V. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savaysa (edoxaban) tablets 15, 30 and 60 mg.

We will be performing additional methods validation studies on Savaysa (edoxaban) tablets 15, 30 and 60 mg, as described in NDA 206316.

In order to perform the necessary testing, we request the following sample materials:

Samples and Reference Standards

10 g edoxaban tosylate drug substance
Particle size distribution X_{10} (b) (4) µ, X_{50} (b) (4) µ, and X90 = (b) (4) µ

10 g edoxaban tosylate drug substance
Particle size distribution X_{10} = (b) (4) µ, X_{50} = (b) (4) µ, and X90 (b) (4) µ

30 Edoxaban tablets 15 mg
30 Edoxaban tablets 30 mg
30 Edoxaban tablets 60 mg
60 Edoxaban tablets 15 mg
60 Edoxaban tablets 30 mg
60 Edoxaban tablets 60 mg (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Yvonne Knight
WO21 RM2667
10903 New Hampshire
Silver Spring, MD 20993-0002

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/07/2014

From: Knight, Yvonne
To: lnelson@dsi.com
Cc: Knight, Yvonne
Subject: (b) (4) Information Request for NDA 206316 (Prompt Response)
Date: Wednesday, July 02, 2014 8:07:06 AM
Importance: High

Good morning Dr. Nelson,

We have an additional information request concerning Daiichi's New Drug Application (NDA) for NDA 206316. We request a prompt response to this IR request no later than **Friday COB July 11, 2014**.

(b) (4) **Concerns**

1. For Figure 1.28. *Decision Tree for Periodical Check* in section 3.2.P.3.4, provide criteria for making "yes" or "no" decisions for "Initial three batches for new or updated model" and "Over defined periods".

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
07/02/2014

From: Nelson, Linda
To: Knight, Yvonne
Cc: Chen, George
Subject: RE: Information Request for NDA 206316 (Teleconference)
Date: Thursday, June 26, 2014 4:19:45 PM

Dear Yvonne,

I am confirming receipt of your email. I have arranged for TC and webex for the meeting (see details below). It would be very helpful if we could present some slides, will you be able to connect to the webex?

Kind Regards,
Linda

******* DO NOT DELETE OR CHANGE ANY OF THE TEXT BELOW THIS LINE *******
You scheduled this meeting.

Meeting Number: (b) (6)
Meeting Password: (b) (6)

To start this meeting
---
1. Go to (b) (6)
.
2. If you are not logged in, log in to your account.

Teleconference information

Provide your phone number when you join the meeting to receive a call back. Alternatively, you can call:
Call-in toll-free number: (b) (6) (US)
Call-in number: (b) (6) (US)
Show global numbers: (b) (6)
Leader PIN (b) (6)
Conference Code: (b) (6)

http://www.webex.com

IMPORTANT NOTICE: This WebEx service includes a feature that allows audio and any documents

and other materials exchanged or viewed during the session to be recorded. You should inform all meeting attendees prior to recording if you intend to record the meeting. Please note that any such recordings may be subject to discovery in the event of litigation.

From: Knight, Yvonne [mailto:Yvonne.Knight@fda.hhs.gov]
Sent: Thursday, June 26, 2014 3:43 PM
To: Nelson, Linda
Cc: Knight, Yvonne; Chen, George
Subject: Information Request for NDA 206316 (Teleconference)
Importance: High

Good afternoon Dr. Nelson,

Per our conversation, we have the following information request concerning Daiichi's New Drug Application (NDA) NDA 206316. We request a teleconference to this IR request for **Tuesday July 1, 2014 10 AM (EST)**.

The information we would like to discuss is as follows:

1. Based on the evaluation of the overall dissolution and clinical data submitted in your original NDA and further amendments, we have the following issues/concerns regarding the proposed dissolution method:

    a. The method does not reflect the (b) (4)

(b) (4)

(b) (4)

We believe that many of these discrepancies are due to the (b) (4)

(b) (4)

2. Based on the above issues/concerns, we recommend that new dissolution methodology showing adequate discriminating ability reflective of meaningful changes in the (b) (4) be developed for your drug product. We remind you that the discriminating ability of a dissolution method is not only determined by the dissolution method testing conditions but also by the selection of the acceptance criterion, which include specification-sampling time point and limit value.

3. Please provide your proposal for pathways to move forward with the review of your proposed drug product.

Please confirm receipt of this Information Request and provide call-in# for the teleconference. Feel free to contact me if you have any questions.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
06/27/2014

From: Nelson, Linda
To: Knight, Yvonne
Cc: Chen, George
Subject: RE (b) (4) Information Request for NDA 206316 (Prompt Response)
Date: Tue June 17, 2014 9:56:18 AM

Dear Yvonne,

I confirm receipt of this information request. We will provide our responses by COB on July 7, 2014.

Kind Regards,
Linda

--
Linda C. Nelson, PhD
Director
Regulatory Affairs-CMC

Daiichi Sankyo, Inc.
399 Thornall Street
Edison, NJ 08837• USA
Phone: + 1 732-590-5000
Mobile (b) (6)
Fax +1 732-906-6652
lnelson@dsi.com
www.dsi.com
Passion for Innovation.
Compassion for Patients.™

From: Knight, Yvonne [mailto:Yvonne.Knight@fda.hhs.gov]
Sent: Tuesday, June 17, 2014 9:52 AM
To: Nelson, Linda
Cc: Chen, George
Subject: (b) (4) Information Request for NDA 206316 (Prompt Response)
Importance: High

Good morning Dr. Nelson,

We have an additional information request concerning Daiichi's New Drug Application (NDA) for NDA 206316. We request a prompt response to this IR request no later than **Monday COB July 7, 2014**.

(b) (4) **Method Development and Validation Concerns**

1. Provide technical details to show how mean areas were calculated by using (b) (4) (Figure 1.125 of section 3.2.P.2.3) that support the conclusion of (b) (4)

(b) (4)

2. For figures 1.136 through 1.138 in section 3.2.P.2.3, provide the measured PC plot including supportive real data to show the measured relative magnitude of the within group vs. between group variability for active tablets and placebo tablets.

3. Clarify whether batch samples used in method validations were representative of the expected process and material variability, and these samples were different from those used in the calibration set.

4. We note that samples from four sites are used in (b) (4) methods validation (DSPP Onahama Plant, DSPP Takatsuki Plant, DSPP (b) (4) and (b) (4) (b) (4). Clarify if the same (b) (4) procedure was used to test the samples from the four sites or each site created identical (b) (4) procedure for the samples at that site. Additionally, provide following information to support your response:

   a. For situations where an identical procedure was created at different sites, whether the same method development, optimization and validation approach was used across sites;

   b. If the calibration model was transferred from one site to another, elaborate how model transfer was carried out.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
06/19/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, June 18, 2014 7:28 AM
To: 'dmorgan@dsi.com'
Cc: 'ggolikov@dsi.com'; Higgins, Janet
Subject: NDA 206316 Savaysa (edoxaban tosylate) - FDA Clinical Information Request

Dear Dr. Morgan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 206316 Savaysa (edoxaban tosylate) tablets, 15, 30, and 60 mg.

We have the following clinical information request:

In your study report for Hokusai VTE we note that on page # 115 Table 11.10 all-cause mortality for the overall study period is shown as 122 in the edoxaban and 106 in the warfarin arm while on page 155 table 12.21 all cause all-cause mortality shown as 136 in the edoxaban and 130 in the warfarin arm. Please explain the discrepancy.

We request a prompt response via email by COB, Friday, June 20, 2014, then follow-up with a formal submission to the NDA.

Janet will be out of the office until June 30, 2014, therefore please email me your response. Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

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/s/

PATRICIA N GARVEY
06/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR PATIENT LABELING REVIEW CONSULTATION**

TO:		FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DMPP-PatientLabelingTeam		Alison Blaus, ODE 1/DCaRP, (301)796-1138
REQUEST DATE: 17 June 2014	NDA/BLA NO.: 206316	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Savaysa (edoxaban) Tablets	Standard	NME	2 Weeks after receiving substantially complete labeling

SPONSOR:	
Daiichi Sankyo	PDUFA Date: 8 January 2015

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☒ ORIGINAL NDA/BLA
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

\\CDSESUB1\EVSPROD\NDA206316\206316.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Since this NDA is a "Split Original" with (b) (4) indications being sought, please file your review to NDA 206316, but link it to Original 1, Original 2 (b) (4)

Filing/Planning Meeting: 14 February 2014

Mid-Cycle Meeting: 12 June 2014 (All disciplines and DCRP-ORIG1 Clinical/Stats) and 17 June 2014 (DHP-ORIG-2 (b) (4) Clinical/Stats)

Labeling Meetings: TBD

Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER: Alison Blaus, RAC

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL (BLAs Only) ☒ DARRTS

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/s/

ALISON L BLAUS
06/17/2014

Executive CAC
Date of Meeting: June 10, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Wendy Schmidt, Ph.D., DAIP, Alternate Member
Thomas Papoian, Ph.D., DABT, DCRP, Team Leader
Baichun Yang, Ph.D., DABT, DCRP, Presenting Reviewer

Author of Draft: Baichun Yang

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA 206316
Drug Name: Savaysa™ (edoxaban) (drug code: DU-176b)
Sponsor: Daiichi Sankyo Inc

Background:

The new drug application (NDA) package for edoxaban (DU-176b, a factor Xa inhibitor) has been submitted to the Agency. The applicant is seeking marketing approval for the drug for the following indications: (i) reduction in the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; (ii) treatment of deep vein thrombosis and pulmonary embolism; (b) (4) The proposed maximal human oral dose is 60 mg/day. The applicant has conducted two-year carcinogenicity studies in mice and rats.

Rat Carcinogenicity Study

The carcinogenicity of the drug DU-176b was assessed in Sprague Dawley rats at oral gavage doses of 0, 60, 200, and 600/400 mg/kg/day for males, and 0, 50, 100, and 200 mg/kg/day for females in a vehicle of 0.5% aqueous methylcellulose. The dose of the high dose male group was reduced to 400 mg/kg during week 44. Dose selection was based on MTDs from a previous 13-week study as follows: early termination due to excessive mortality for the 1500 mg/kg/day dose group, one male death at the 600 mg/kg/day dose (1/10 males), and alopecia and sores/scabs in females only at 200 and 600 mg/kg/day. The Exec CAC previously concurred with selection of the high doses.

In the two-year carcinogenicity study, mortality was significantly higher in males at the dose of 600/400 mg/kg/day. There was a higher incidence and greater severity of centrilobular hepatocellular degeneration/necrosis in males at 600/400 mg/kg/day. Liver centrilobular hepatocellular degeneration/necrosis may be the cause of 8 of the 50 unscheduled male deaths in the 600/400 mg/kg/day males. There were bleeding or bleeding-related findings, such as slightly, but statistically lower red cell counts in females at 200 mg/kg/day, higher incidences of red oral and nasal discharge, and red haircoat in males at 600/400 mg/kg/day and females at 200

mg/kg/day. There was no evidence of increased neoplasia at any dose level. Systemic exposures at NOAELs for carcinogenicity in male and female rats are estimated to be 8 and 14 times, respectively, the maximum recommended human daily dose of DU-176b based on $AUC_{0\text{-}24\ hr}$ comparisons.

Mouse Carcinogenicity Study

The carcinogenicity of DU-176b was assessed in CD-1 male and female mice at oral gavage doses of 0, 50, 150, 500 mg/kg/day in a vehicle of 0.5% aqueous methylcellulose. Dose selection was based on an MTD from a previous 13-week mouse study as follows: early termination due to excessive mortality for the 1500 mg/kg/day dose group, and lower body weight gain and food consumption, hunched posture, and squinted eyes at 600 mg/kg/day. The Exec CAC previously concurred with selection of the high dose.

Higher mortality was noted for males at the dose 500 mg/kg/day and for females at the dose 150 mg/kg/day. About 10% lower mean body weight was observed in males at 500 mg/kg/day, and a lesser extent of lower body weight was also seen in females at 500 mg/kg/day. None of the numerically increased tumor incidences showed statistically significant dose-response relationships. Systemic exposures at NOAELs for carcinogenicity in male and female rats are estimated to be 3 and 6 times, respectively, the maximum recommended human daily dose of DU-176b based on $AUC_{0\text{-}24hr}$ comparisons.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms in the study.

Mouse:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/NDA 206316, DCRP, DHOT
/Thomas Papoian, DCRP
/Baichun Yang, DCRP
/Alison Blaus, DCRP
/Janet Higgins, DHOT
/Adele Seifried, OND IO

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/s/

ADELE S SEIFRIED
06/12/2014

ABIGAIL C JACOBS
06/12/2014

From: Nelson, Linda
To: Knight, Yvonne
Cc: Chen, George
Subject: RE: Information Request for NDA 206316 (Prompt Response)
Date: Monday, June 02, 2014 4:03:12 PM

Dear Yvonne,

I am confirming receipt of your email and we will provide you with a courtesy copy of the submission when it is sent through the gateway at FDA.

Kind Regards,
Linda

From: Knight, Yvonne [mailto:Yvonne.Knight@fda.hhs.gov]
Sent: Monday, June 02, 2014 3:43 PM
To: Nelson, Linda
Cc: Chen, George
Subject: Information Request for NDA 206316 (Prompt Response)
Importance: High

Good afternoon Dr. Nelson,

We have an additional information request concerning Daiichi's New Drug Application (NDA) for NDA 206316. We request a prompt response to this IR request no later than **Monday COB June 16, 2014**.

Drug Substance Specification:

1. We do not agree with your proposed removal of the following residual solvents from drug substance specification. You may, however, request the removal of any specific attribute from drug substance specification during the life cycle of the product with adequate supporting information. At this stage, we recommend that you include following residual solvents in drug substance specification with appropriate acceptance criteria and test methods:

(b) (4)

(b) (4)

2. You have not provided any justification for the acceptable level of genotoxic impurity

in drug substance. Justify the proposed specification (Total NMT [redacted] ppm) for [redacted]

Drug Substance Manufacturing:

3. We have following comments on the revised drug substance manufacturing information submitted on 30-Apr-2014:

a) [redacted] than proven acceptable range ensuring that the actual manufacturing operation is not close to the edge of failure. However, most of your [redacted] provided in the Flow Chart for Manufacturing Fig. 2 to Fig. 13 in Sec 3.2.S.2.2, is the same as [redacted]. We recommend that you revise [redacted] at minimum for the important process parameters [redacted] Include justification for the proposed ranges with experimental data (if available).

b) Your statement in Sec 3.2.S.2.2 page 12 - [redacted] - is not acceptable. We do not have adequate information in the submission to allow for future quality assurance flexibility based on the proposed [redacted] Remove the statement from the submission and provide the following statement that "*any significant changes of the important process parameters from the set point will be reported to the Agency using the appropriate regulatory mechanism*." Please note that significant changes are defined as the changes which can impact the quality.

c) In the Flow Chart for Manufacturing Fig 2-13 in Sec 3.2.S.2.2, use the following footnote for [redacted]:

[redacted] *is provided for informational purposes only and not to implement any changes of the process parameters*."

Best Regards,

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment

FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
06/03/2014

From:	Higgins, Janet
To:	Morgan, Doreen; Golikov, Gretchen (ggolikov@dsi.com)
Cc:	Higgins, Janet
Subject:	NDA 206316:Edoxaban Information Request
Date:	Tuesday, May 20, 2014 1:58:06 PM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

Please refer to Table 10.9 in the study report for Hokusai VTE regarding time in various INR ranges. Prepare a comparable table for each of the following warfarin patient arm subpopulations:

- Patients who were treated for ≤3 months
- Patients who were treated 3 to 6 months
- Patients who were treated for >6 months.

Please also submit datasets, programs used to generate the requested tables and necessary documentations for our statistical team to verify the analysis results.

Please respond **by Tuesday, May 27, 2014**.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
05/21/2014

PeRC PREA Subcommittee Meeting Minutes
May 7, 2014

PeRC Members Attending:
Lynne Yao
George Greeley
Hari Cheryl Sachs
Tom Smith
Karen Davis-Bruno
Andrew Mosholder
Lily Mulugeta
Robert "Skip" Nelson
Dianne Murphy
Daiva Shetty
Peter Starke
Susan McCune
Coleen LoCicero

PREA

(b) (4)

10:50	NDA	206316	Savaysa (edoxaban) Deferral/Plan (**Agreed iPSP obtained**)	Indicated for the treatment of deep vein thrombosis (DVT) and Pulmonary embolism (PE) (b) (4)
	NDA	*206316*	*Savaysa (edoxaban) Full Waiver*	*To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation*

(b) (4)

(b) (4)

(b) (4)

Savaysa Deferral/Plan

- NDA 206316 seeks review of Savaysa (edoxaban) for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)
- The application has a PDUFA goal date of January 8, 2015.
- The product triggers PREA as a new: active ingredient, indication, dosage form, dosing regimen, and route of administration.
- *PeRC Recommendations:*
    - The PeRC agreed with the Division to grant a deferral because adult studies are completed and the product is ready for approval in adults. The PeRC also acknowledged that this product has an Agreed iPSP and that the plan for pediatric studies has not changed upon submission of the marketing application.
    - The PeRC noted that this is the first application in which an Agreed iPSP is being used as the pediatric plan.

Savaysa Full Waiver

- NDA 206316 seeks review of Savaysa (edoxaban) for the reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation.
- The application has a PDUFA goal date of January 8, 2015.
- The product triggers PREA as a new: active ingredient, indication, dosage form, dosing regimen, and route of administration.
- *PeRC Recommendations:*
    - The PeRC agreed with the Division to grant a full waiver of pediatric studies because studies would be impossible or highly impractical. The PeRC also acknowledged that this product has an Agreed iPSP and that the plan for pediatric studies has not changed upon submission of the marketing application.
    - The PeRC noted that this is the first application in which an Agreed iPSP is being used as the pediatric plan.

(b) (4)

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

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/s/

GEORGE E GREELEY
05/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
Mail: OSE – Liver Team	Alison Blaus/Cardiovascular & Renal Products/(301) 796-1138

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6May14	77254	206316	New Drug Application (NDA)	8 January 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
SAVAYSA (edoxaban)	Standard Review	NME	8 August 2014

NAME OF FIRM: Daiichi-Sankyo

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- × SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This consult is for review of the liver data included in the NME NDA edoxaban. This submission was received on 8Jan14 and includes data to support the following (b) (4) indications (registration study for the indication in parentheses):

ORIG-1: Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation (ENGAGE TIMI 48 Study - #DU176b-C-U301)

ORIG-2: Treatment of Deep Vein Thrombosis & Pulmonary Embolism (HOKASAI-VTE Study - #DU176b-C-U305)

(b) (4)

The liver data for both of these studies was submitted shortly after the initial submission, but on a CD per the EDISH specifications (it has been uploaded to EDISH). We have been in communication with OSE regarding this NDA and have been working with John Senior, Mark Avignan, and Ted Guo. This NDA is eCTD and can be found in the EDR. We have a mid-cycle meeting for 11June14 and no AC. We are requesting your review to be completed and in DARRTS one month ahead of the primary clinical review, so that it can be taken into account in their final review. The CDTLs on this application are Martin Rose (for the atrial fibrillation indication – ENGAGE study) and Kathy Gobie-Suh (for the DVT/PE indications – HOKASAI study). The clinical reviews on this application are Melanie Blank (efficacy reviewer for ENGAGE), Tzu-Yun McDowell (safety reviewer for ENGAGE), and Saleh Ayache (safety/efficacy reviewer of HOKASAI). Please do not hesitate to contact me, the CDTLs, or any of the primary clinical reviewers should you need anything. Thank you in advance! Alison

SIGNATURE OF REQUESTER: Alison Blaus	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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
05/06/2014

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

NOTE: This template document for Pediatric Deferral Request for NDA 206316 relates only to the indications being reviewed by the Division of Hematology Products (DHP) for this new NDA.

BACKGROUND
Please check all that apply: ☐ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☒ **Deferral/Pediatric Plan**

BLA/NDA#: 206316

PRODUCT PROPRIETARY NAME: Savaysa **ESTABLISHED/GENERIC NAME:** edoxaban tosylate

APPLICANT/SPONSOR: Daiichi-Sankyo

PREVIOUSLY APPROVED INDICATION/S:
(1) none
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
(1)to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [being reviewed by the Division of Cardiovascular and Renal Products]
(2) for the treatment of deep vein thrombosis (DVT) and Pulmonary embolism (PE)_[being reviewed by DHP]
(b) (4)
(4) _____

BLA/NDA STAMP DATE: 1/8/2014

PDUFA GOAL DATE: 1/8/2015 **SUPPLEMENT TYPE**: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☒ ***active ingredient(s) (includes new combination);*** ☒ ***indication(s);*** ☒ ***dosage form;*** ☒ ***dosing regimen; or*** ☒***route of administration?***

This is the initial NDA submission for a new drug.

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒

If Yes, PMR #_____ NDA #_____

Does the division agree that this is a complete response to the PMR? Yes ☐ ***No*** ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived.

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from adult-related conditions on the next page

   ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. Provide justification for Waiver:

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign Prostatic Hyperplasia
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment
Actinic Keratosis

Cancer:
Basal cell
Bladder
Breast
Cervical
Colorectal
Endometrial
Gastric
Hairy cell leukemia
Lung (small & non-small cell)
Multiple myeloma
Oropharynx (squamous cell)
Ovarian (non-germ cell)
Pancreatic
Prostate
Renal cell
Uterine

DEFERRAL REQUEST

Please attach:

☒ ***Pediatric Record***

1. **Age groups included in the deferral request: birth to < 18 years**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval

4. **Provide projected date for the submission of the pediatric assessment (deferral date): _____June 2022_____**

5. **Did applicant provide certification of grounds for deferring assessments? ☒ Yes ☐ No**

The sponsor provided rationale and timeframe for their studies.

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? ☒ Yes ☐ No**
   Proposed timeline appears reasonable.

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency? ☒ Yes ☐ No**

The sponsor submitted an initial Pediatric Study Plan (PSP) to DHP on 6/4/2013 (IND 63266). The Division provided comments and recommendations from DHP to the sponsor on 8/16/2013. The sponsor submitted a revised PSP (Agreed-Upon Initial PSP) to DHP on 10/1/2013. On 10/31/2013 DHP issued a letter to the sponsor confirming DHP agreement to the submitted Agreed-Upon Initial PSP.

2. Does the division agree with the sponsor's plan? ☐ **Yes** ☐ **No**
Based on our initial review of the NDA, we will propose modifications to the Sponsor's plan to include a study to address extended prophylaxis beyond 6 months.

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? ☒ **Yes** ☐ **No**

Table 5: Timeline of Pediatric Development Plan

Study Ref #	Study Short Title	Start Date (FPI)	Completion Date (LPLV)	CSR Available
1	Relative Bioavailability/ Food Effects Study of Edoxaban Peds Formulation	June 2013	December 2013	June 2014
2	Pediatric PK/PD Study	June 2014	December 2016	June 2017
3	Phase 3 Pediatric VTE Study	December 2016	December 2021	June 2022

4. Has a Written Request been issued? ☐ **Yes** ☒ **No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. Has a PPSR been submitted? ☐ **Yes** ☒ **No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Clinical Studies:

Study 1: Relative Bioavailability/Food Effects Study of an Edoxaban Pediatric Formulation (open-label, randomized, 3-way crossover). The study was started on June 2013. The study will enrolled 24 adult subjects. The purpose of this study is to characterize PK of edoxaban oral suspension, assess relative bioavailability vs oral tablet; assess food effects and palatability of pediatrics formulation.

Study 2: Title: "A Phase 1, Open-Label, Single-Dose, Non-Randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients." The protocol under review. The study proposes to start in June 2014. The study will enrolled (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 phase 3 trial.

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

Age group and population (indication) in which study will be performed:

Study 1:
__Healthy adults_____

Study 2:
___Age groups (birth to < 2 yrs, 2 to < 6 yrs, 6 to < 12 yrs, 12 to < 18 yrs)__at risk of recurrent VTE, recently completed anticoagulation therapy, or cardiac patients who may need anticoagulation_____

Study 3:

____Pediatric patients ages 36 weeks gestational to <18 years with documented VTE. _____

This section should list the age group and population exactly as it is in the plan.

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Study 1:
_____24_____

Study 2:
____ (b) (4) [Based on protocol submitted to IND 63266 on 2/19/2014 the sponsor proposes the following age cohorts and dose groups:

- 12 to < 18 years of age (12 patients)
  - Cohort 1a: Low dose group (6 patients)
  - Cohort 1b: High dose group (6 patients)
- 6 to < 12 years of age (12 total patients)
  - Cohort 2a: Low dose group (6 patients)
  - Cohort 2b: High dose group (6 patients)
- 2 to < 6 years of age (12 total patients)
  - Cohort 3a: Low dose group (6 patients)
  - Cohort 3b: High dose group (6 patients)
- 0 to < 2 years of age (12 total patients)
  - Cohort 4a: Low dose group (6 patients)
  - Cohort 4b: High dose group (6 patients)

Study 3:
(b) (4)

Entry criteria:

Study 1:
Healthy male and female adult volunteers
Subjects should not have history or evidence of clinically significant cardiac, hepatic, renal, pulmonary, endocrine, neurologic, infectious, gastrointestinal, hematologic, or oncologic disease. Subjects should not have history of bleeding or use of any drugs or substances known to be strong inhibitors or strong inducers of CYP 3A4/5 enzymes or P-gp within 28 days prior to the first dose of study treatment

Study 2:
Inclusion:

- Pediatric patients (0 to < 18 yrs of age) at risk of recurrent VTE
- Patients that are recently completing their standard of care anticoagulation therapy
- Cardiac patients who may need anticoagulation

Exclusion:

- Any major or clinically relevant bleeding during prior anticoagulant therapy
- Subjects with renal function <50% of normal for age and size
- Subjects with severe hepatic impairment
- Subjects with history of peptic ulcer or gastrointestinal bleeding
- Subjects with malabsorption disorders (eg. Cystic fibrosis, short bowel syndrome)

Study 3:
(b) (4)

(b) (4)

Clinical endpoints:

Study 1:
The primary endpoints will include characterization of the single-dose PK of edoxaban, assessment of relative bioavailability, and assessment of effect of food on the rate and extent of edoxaban absorption when edoxaban is dosed as a liquid suspension with or without food.

Study 2:
The endpoints of the study are to determine the pharmacokinetic (PK) of edoxaban, PD biomarkers, and the visual analog scale (VAS) for palatability.

Study 3:
(b) (4)

Timing of assessments:

Study 1:
_____after dosing_____

Study 2:
after dosing_____

Study 3:
_____after 3 months (+3 days) of treatment_____

Statistical information (statistical analyses of the data to be performed):

Study 1:
___Not described_____

Study 2:
Plasma concentration-time data for edoxaban and metabolites will be plotted for each individual and summarized by age cohort and/or dose group, and measurement time interval, as appropriate. Concentration-time data will be analyzed using model-based approaches such as nonlinear mixed-effects modeling, where data from other studies may be pooled with pediatric data, and PK parameters will be calculated. Estimated PK parameters will be used to assess age dependencies. Estimated PK parameters will be summarized by age cohort and/or dose group using descriptive statistics._____

Study 3:
(b) (4)

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☒ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☒ **No**

Will a DSMB be required? ☐ **Yes** ☒ **No**

Other comments:

Division comments on product efficacy:

The application for the indications in adults is under review. The initial review of the pivotal trial revealed that edoxaban is non-inferior to warfarin for the treatment of VTE (b) (4)

Division comments on sponsor proposal to satisfy PREA:
The Sponsor's proposal plan is to conduct 3 trials: 1) A phase 1 biopharmaceutical trial to assess the relative bioavailability and the food effect on edoxaban adsorption dosed as a liquid suspension, 2) A phase 1 single dose trial (dose finding) to determine the PK/PD of edoxaban in pediatric population and determine the dose for the phase 3 trial, 3) A phase 3 trial in pediatric patients with VTE to determine the safety and efficacy of edoxaban for treatment of VTE. This plan was discussed with the sponsor during 2013 and DHP agreed with the applicant on the initial Pediatric Study plan (PSP) on October 15, 2013.

DHP finds the applicant plan may not be adequately satisfy PREA requirements based on the NDA submission currently under review. For the current NDA submission the sponsor has submitted a single study for the treatment of VTE including DVT and PE (b) (4) the Hokusai VTE Study). Duration of treatment in the study was 3, 6 or 12 months as determined by the sponsor. (b) (4) Unlike other applications where patients were re-randomized at completion of "treatment" of index VTE, in this study patients merely continued therapy for a longer time. About 61% of patients received treatment for >6 months and 40% for >12 months. Considering that usually 6 months is the upper end of duration for treatment of confirmed VTE. (b) (4)

The Sponsor has asked (b) (4)

(b) (4)

The applicant requested a deferral for pediatric assessment in VTE until after the NDA approval. The applicant rationale for deferral request is that it is more appropriate to obtain sufficient data demonstrating a positive benefit/risk profile for edoxaban in adult prior to initiating studies in pediatric population.

Any additional comments: DHP is in favor of granting the deferral of initiating the proposed phase 3 trial in pediatric population until after the approval. However, the initiation of the planned bioavailability trial and single-dose PK trial need not await NDA approval for the indication in adults.

PeRC ASSESSMENT TEMPLATE

Please attach:

- ☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***
- ☐ ***Pediatric Record***

Date of PREA PMR:
Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration**: *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*
Types of Studies/ Study Design: *Example:* *Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.* *Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*
Age group and population in which study/ies was/were performed: *Example:* *Study 1: patients aged X to Y years.* *Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.*
Number of patients studied or power of study achieved: *Example:* *Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.* ***Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .***
Entry criteria: This section should list pertinent inclusion/exclusion criteria. *Example:* *Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs* *Patients had a negative pregnancy test if female.*

Clinical endpoints: *Example:* *Study 1: Clinical outcome and safety were the primary endpoints.* *Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*
Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted. *Example:* *Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.* *Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*
Timing of assessments: *Example:* *Baseline, week 2, week, 6, and end of treatment*

Division comments and conclusions (Summary of Safety and Efficacy)
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

JANET G HIGGINS
05/05/2014

From:	Knight, Yvonne
To:	lnelson@dsi.com
Cc:	Knight, Yvonne
Subject:	Additional Information Request for NDA 206316 (Prompt Response)
Date:	Friday, May 02, 2014 12:57:53 PM
Importance:	High

Good Afternoon Dr. Nelson,

We have an additional information request concerning Daiichi's New Drug Application (NDA) for NDA 206316. We request a prompt response to this IR request no later than **Friday COB May 9, 2014**.

1. Establish an appropriate range with justification for tablet hardness. Provide supportive data for the proposed range, particularly focusing on its effect on dissolution. The dissolution data should include dissolution profiles for all strengths as a function of tablet hardness within and outside the proposed range.

Best Regards,

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
05/02/2014

From: Knight, Yvonne
To: lnelson@dsi.com
Cc: Knight, Yvonne
Subject: Information Request for NDA 206316 (Prompt Response)
Date: Wednesday, April 30, 2014 3:15:06 PM
Importance: High

Good Afternoon Dr. Nelson,

We have an information request concerning Daiichi's New Drug Application (NDA) for NDA 206316. We request a prompt response to this IR request no later than **Friday COB May 9, 2014**.

1. The following requests are referenced to Section 2.3 P. 3.2: Manufacturing Process Development.
   a. Confirm the evaluated ranges of each material attribute or process parameter in the following tables are derived from the proposed commercial scale manufacturing process.

      Table 1.115, Table 1.134, Table 1.143, Table 1.150, Table 1.160.

   b. As we cannot locate all the ranges in the above tables, clearly indicate where the information is located in the submission.

2. For [redacted] (b) (4), provide information that supports the use of [redacted] (b) (4)

Best Regards,

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
04/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

METHODS VALIDATION
MATERIALS RECEIVED

Daiichi Sankyo, Inc.
Attention: Doreen V. Morgan, Pharm.D., Executive Director, Regulatory Affairs
399 Thornall Street
10th floor
Edison, NJ 08837

Dear Doreen Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savaysa (edoxaban), tablets 15, 30 and 60 mg and to our March 6, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on April 17, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

MICHAEL L TREHY
04/17/2014

From:	Knight, Yvonne
To:	"lnelson@dsi.com"
Cc:	Chen, George (gchen@dsi.com)
Subject:	Information Request for NDA 206316 (Prompt Response)
Date:	Wednesday, April 16, 2014 9:35:00 AM
Importance:	High

Good Morning Dr. Nelson,

We have an information request concerning Daiichi's New Drug Application (NDA) for NDA 206316. We request a prompt response to this IR request no later than **Friday COB April 18, 2014**.

1. Submit the control stream files, raw data, and the inputs and outputs used/generated for the dissolution model development and validation. These data should be submitted as SAS transport files or JMP files.

Best Regards,

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
04/16/2014

From:	Higgins, Janet
To:	Golikov, Gretchen; Morgan, Doreen
Cc:	Higgins, Janet
Subject:	RE: NDA 206316: Edoxaban --ORG-2 (b) (4) clinical information request format clarification
Date:	Thursday, April 10, 2014 12:40:29 PM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

In response to your email inquiry dated April 4, 2014, please provide more granularity in the Demographics Listing in the column 'Risk Factors' , i.e., rather than putting just 'other' or 'temporary', list the specific risk factors each patient has [e.g., previous VTE, thrombophilia, prolonged immobilization, etc.]

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

From: Golikov, Gretchen [mailto:ggolikov@dsi.com]
Sent: Friday, April 04, 2014 2:13 PM
To: Higgins, Janet
Cc: Morgan, Doreen
Subject: RE: NDA 206316: Edoxaban --ORG-2 (b) (4) clinical information request format clarification

Hi Janet,
Per your request, attached are 6 sample listings for review.

Please let us know if these listings are acceptable, and then we will generate the full listings.

Have a great weekend!

--

Gretchen Golikov

Director
Regulatory Affairs

Daiichi Sankyo, Inc.
399 Thornall Street
Edison, NJ 08837• USA
Phone: + 1 732-590-4986
Fax +1 732 906 6652
ggolikov@dsi.com
www.dsi.com

Passion for Innovation.
Compassion for Patients.™

From: Morgan, Doreen
Sent: Tuesday, April 01, 2014 9:39 AM
To: Higgins, Janet
Cc: Golikov, Gretchen
Subject: RE: NDA 206316: Edoxaban --ORG-2 (b) (4) clinical information request format clarification
Importance: High

Dear Janet,

Thanks for the clarification on our questions to the FDA regarding your requested information. We will meet with our team here and communicate the clarifications and work to get you the sample listings by Friday.

I will be out of the country traveling for business the rest of this week so please contact Gretchen Golikov at ggolikov@dsi.com directly during my time away from the office, but please continue to copy me. I have also copied Gretchen on this email as well.

Kind regards

Doreen

From: Higgins, Janet [mailto:Janet.Higgins@fda.hhs.gov]
Sent: Tuesday, April 01, 2014 8:54 AM
To: Morgan, Doreen
Cc: Higgins, Janet
Subject: NDA 206316: Edoxaban --ORG-2 (b) (4) clinical information request format clarification

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

In response to your inquiry dated Monday, March 24, 2014 desiring additional clarification on the clinical information request regarding the the Hokusai VTE Study, several listings tables will be needed. At a minimum these should include:

- General patient info (subj#; site; country; treatment arm; included in safety pop?; included in mITT pop; included in protocol-defined primary analysis pop?; included in per protocol pop?, etc.)

- Demographic Info (subj#; Age; gender; treatment arm; race; weight; body mass indes; creatinine clearance; etc)

- Baseline characteristics (subj#; treatment arm; dx VTE; DVT?; PE?; VTE location?; symptoms?; risk factors; previous episode of VTE; known thrombophilic condition; relevant med hx; relevant CRF comments, etc.)

- Disposition (subj#; treatment arm; completed treatment?; completed followup?; duration of study treatment of index event; duration of anticoagulant therapy prior to randomization; endpoint event (DVT/PE); adverse event (list); reason discontinued; etc.)

- Efficacy data (subj #; treatment arm; DVT?, PE?; death; Compliance; INR; etc.)

- Any serious adverse event (subj#; treatment arm; event; day of event; outcome; intervention; treatment interrupted/stopped, etc.)

Subset each table by treatment (or have a separate table for each treatment [then you need include treatment only in the table header/title and not also as a field]). Try to keep tables within margins of a single landscape display page. If more than one page is needed for an individual patient listing for a particular table, include the patient number on each page. (Note: If any subject numbers are not unique for the study, site will also need to be included in each table). Note that the tables should be presented as pdf files as are the other listings tables you have submitted thus far.

We agree that some of the baseline characteristics for the patients are included in the index event listing (16.2.1.1) that was submitted on 3/10/2014. This listing does not, however, appear to include information about baseline risk factors or other relevant medical history. [Note: It is not clear to us why this listing was submitted under heading of Adverse Event Listings].

In the original submission (1/8/2014) the Adverse Events listings folder contains a collection of listings for selected adverse events (including efficacy endpoint events and bleeding). While these generally appear appropriate, it is also seems clear that the listings when considered in total are not comprehensive. The listing that includes the efficacy outcomes does not include any other relevant information such as INR, time in therapeutic range (warfarin), or compliance.

The 'Compliance' listing included in the 1/8/2014 submission appears to include only those patients who had INR $\geq$5 at some point during the study. The sponsor should provide a listing that includes a more comprehensive presentation of INR values for patients who had an bleeding or efficacy endpoint, preferably in conjunction with efficacy outcome.

Please send us a sample page or two of each table before generating the entire listing via email by

Friday, April 4, 2013. A new proposed timeline for the entire submission may be proposed once there is an understanding of the information that has been requested.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
04/11/2014

From:	Higgins, Janet
To:	Morgan, Doreen
Cc:	Higgins, Janet
Subject:	NDA 206316: Edoxaban --ORG-2 (b) (4) clinical information request format clarification
Date:	Tuesday, April 01, 2014 8:54:12 AM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

In response to your inquiry dated Monday, March 24, 2014 desiring additional clarification on the clinical information request regarding the the Hokusai VTE Study, several listings tables will be needed. At a minimum these should include:

- General patient info (subj#; site; country; treatment arm; included in safety pop?; included in mITT pop; included in protocol-defined primary analysis pop?; included in per protocol pop?, etc.)

- Demographic Info (subj#; Age; gender; treatment arm; race; weight; body mass indes; creatinine clearance; etc)

- Baseline characteristics (subj#; treatment arm; dx VTE; DVT?; PE?; VTE location?; symptoms?; risk factors; previous episode of VTE; known thrombophilic condition; relevant med hx; relevant CRF comments, etc.)

- Disposition (subj#; treatment arm; completed treatment?; completed followup?; duration of study treatment of index event; duration of anticoagulant therapy prior to randomization; endpoint event (DVT/PE); adverse event (list); reason discontinued; etc.)

- Efficacy data (subj #; treatment arm; DVT?, PE?; death; Compliance; INR; etc.)

- Any serious adverse event (subj#; treatment arm; event; day of event; outcome; intervention; treatment interrupted/stopped, etc.)

Subset each table by treatment (or have a separate table for each treatment [then you need include treatment only in the table header/title and not also as a field]). Try to keep tables within margins of a single landscape display page. If more than one page is needed for an individual patient listing for a particular table, include the patient number on each page. (Note: If any subject numbers are not unique for the study, site will also need to be included in each table). Note that the tables should be presented as pdf files as are the other listings tables you have submitted thus far.

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clear to us why this listing was submitted under heading of Adverse Event Listings].

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The 'Compliance' listing included in the 1/8/2014 submission appears to include only those patients who had INR ≥5 at some point during the study. The sponsor should provide a listing that includes a more comprehensive presentation of INR values for patients who had an bleeding or efficacy endpoint, preferably in conjunction with efficacy outcome.

Please send us a sample page or two of each table before generating the entire listing via email by **Friday, April 4, 2013**. A new proposed timeline for the entire submission may be proposed once there is an understanding of the information that has been requested.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
04/01/2014

From:	Higgins, Janet
To:	Morgan, Doreen
Cc:	Higgins, Janet
Subject:	clinical information request for NDA 206316: Edoxaban --ORG-2 (b) (4)
Date:	Friday, March 21, 2014 1:22:02 PM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We have the following comment regarding the Hokusai VTE Study:

It appears that no listings have been provided for demographic data, prior medical history (including VTE risk factors such as prior history of thromboembolic events), baseline disease characteristics, individual efficacy data or individual laboratory measurements by patient. Please provide these listings. If possible, provide the listings including all randomized patients in table form (i.e., with major headings such as subject #, age and gender, study endpoint bleeds, study endpoint DVT, study endpoint PE, etc. across the page as columns and individual patients as rows. (Several tables of this type may be necessary. Try to group related data within the individual tables, e.g., age and gender should be in the same table).

Please respond **by Friday, March 28, 2014**.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

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/s/

JANET G HIGGINS
03/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1
NDA 206316/Original 2
(b) (4)

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) dated 8 January 2014, received 8 January 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to your amendments dated January 14, 21, and 31, February 3 (two), 10 (two), 14 (three), 18, 19, 20 (two), 21, 24, 25, 26, 27, and 28, March 6 (two), 10 (two), 12, and 13, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is **January 8, 2015**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **September 27, 2014**. In addition, the planned date for our internal mid-cycle review meeting is **June 11, 2014**. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing & Controls
Regarding the Drug Product:

1. (b) (4)

2. **Analytical methods for Control strategy:** You have proposed multiple analytical methods for the control strategy for several material attributes such as (b) (4) While your first method to control these properties during manufacturing is (b) (4) you have not explained when and why the (b) (4) methods such as (b) (4) will be used. Additionally, no information has been provided on how (b) (4) control will be applied during the process when you use such (b) (4) analytical methods. Provide appropriate clarification/justification.

(b) (4)

(b) In your studies (Ref. Tab 1.45, 1.2.2.3., Section 3.2.P.2.3) (b) (4)

(b) (4)

Regarding the Drug Substance:

8. Your proposed (b) (4) for the manufacture of edoxaban tosylate are not supported by adequate information (b) (4) We recommend the use of (b) (4) ts only for the description of drug substance manufacturing process.
9. (b) (4)

(b) (4)

10. If edoxaban undergoes change in its (b) (4) provide data indicating that the process is controlled by either:

(b) (4)

(b) (4)

Clinical – Atrial Fibrillation (ORIG1)

1. We note that more than one analysis dataset under Sequence 0009 (dated February 18, 2014) is incomplete. For example, the adverse event dataset (AE.xpt) under the analysis dataset folder is incomplete with only 1588 observations with adverse events compared to 135988 records in sequence 0003 (dated February 3, 2014). Please QC all datasets in Sequence 0009 to make sure the most recent versions of all datasets (both STDM and analysis datasets) are correct.
2. We note several issues below related to the laboratory dataset (LB.xpt). Please address all comments and resubmit the dataset. Considering the large size of the dataset, you can submit separated laboratory datasets stratified by type - chemistry, hematology, serology, urinalysis and others:

a) There is a small percentage of lab data that had missing values for LABSTRESC, when LBORRES was provided.
b) For subjects who had UREA data instead of BUN data, please convert UREA data to BUN data with the same units and only use BUN as the lab test name.
c) Some data values for variable VISIT were not listed in the define file (e.g. MONTH 6 QLAB UNSCHEDULED V4). Please explain these values using plan language.
d) Two subjects (DU176b-30630008, DU176b-38120006) had data entries in the laboratory dataset but did not have data entries in the demographic dataset (DM.xpt).

3. We observed a few subjects that had a study start date (CTSTDTC) after the study end date (CTENDTC) in the CM and CT datasets. Please clarify if these are data entry errors, and if so, please correct them.
4. The FDA requested bleeding dataset (blddata.xpt) is not in a format previously agreed. The dataset should be set up to allow time to event analyses for all adjudicated bleeding events. Please include subjects without a bleeding event in the dataset. Subjects without a bleeding event of interest should be censored at the earliest day of death, last dose+3 days or last known information about the event of interest.
5. We observed a few subjects in the listing of study drug by lot number dataset (sdlot.xpt) that contain a blank value for SITEID. Please QC the dataset and correct the blank values. Please also include the variable USUBJID in the dataset.

Clinical – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2) (b) (4)

1. Please note that the organization of the clinical section (Module 5) of the NDA submission is somewhat confusing and navigation is somewhat cumbersome (for example, scanty linking and some links that are provided are not highlighted in the text). It is likely that there will be a number of requests for information and clarification during the review.

2. The bleeding dataset is not formatted to allow time to event analyses for all adjudicated bleeding events. Subjects who did not have a bleeding event are not included in the dataset. Please provide a revised dataset that includes all randomized subjects, including those without a bleeding event. Also include the arm of randomization, the start date and end date of treatment in the same data set. Please provide time to event analyses for bleeding (or if these are already provided, please direct). Subjects without a bleeding event of interest should be censored at the earliest day of death, last dose +2 days or last known information about the event of interest.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. Please refer to the Revision Date in Highlights Section: *The revision date is not listed in the following format: "Revised: 1/2014" but rather is listed as: "Revised: Mon 20XX". Please revise to reflect the proper format.*
2. Please refer to the Adverse Reactions in Highlights Section: Insert the correct information in the following portions that are currently listed: <<Insert manufacturer>> at <<Insert phone No. and Web address>>.

We request that you formally resubmit labeling (in Microsoft Word format) that addresses these issues by **April 11, 2014.** The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application for ORIG-1. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We also acknowledge receipt of your request for a full deferral of pediatric studies for this application for ORIG-2 (b) (4) Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, please call the following Regulatory Project Managers:

For NDA 206316/Original 1 – Alison Blaus, RAC at (301) 796-1138
For NDA 206316/Original 2 – Janet Higgins at (240) 402-0330
(b) (4)

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
03/21/2014

ANN T FARRELL
03/21/2014

From:	Higgins, Janet
To:	Morgan, Doreen
Cc:	Higgins, Janet; Blaus, Alison
Subject:	clinical study site Information request for NDA 206316: Edoxaban
Date:	Tuesday, March 18, 2014 2:15:31 PM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We continue to review your NDA and request additional information regarding Protocol 305 Site 1039 (Edwin Kingsley, M.D., Las Vegas, NV) in PDF electronic format:

The study subject data listings should capture the following, as applicable:
(1) subject discontinuation (If applicable per treatment group: site subject number, screening visit date, informed consent date, assent date, date of first dose/last dose, length of date of discontinuation, reason for discontinuation).
(2) prior and concomitant medications (non-study medications): (If applicable per treatment group: site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.
(3) prohibited medications (non-study medications): as above with concomitant medications
(4) adverse events, (If applicable per treatment group: preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no)).
(5) primary efficacy endpoint (recurrent venous thrombo-embolic event/s) (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1…etc).
(6) primary safety endpoint: clinically relevant bleeding (i.e., major or clinically relevant non-major bleeding) occurring during treatment or within 3 days after interrupting or stopping study drug (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1…etc).

Please respond by **March 24, 2014**. Please send your response via email followed by an official response sent to ORG-2 (b) (4) of NDA 206316.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
03/18/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206316/Original 1
NDA 206316/Original 2
(b) (4)

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Daiichi Sankyo, Inc.
399 Thornall Street
10th Floor
Edison, NJ 08837

ATTENTION: Doreen V. Morgan, Pharm.D.
Executive Director, Regulatory Affairs

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) dated and received January 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edoxaban Tablets, 15 mg, 30 mg, and 60 mg.

We also refer to your January 21, 2014, correspondence, received January 22, 2014, requesting review of your proposed proprietary name, Savaysa. We have completed our review of the proposed proprietary name, Savaysa, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 21, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Bengtson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3338. For any other information regarding this application, contact Alison Blaus, Regulatory Project Manager in the Division of Cardiovascular and Renal Product, at (301) 796-1138 or Janet Higgins, Regulatory Project Manager in the Division of Hematology Products, at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316 **INFORMATION REQUEST**

Daiichi Sankyo Inc.
Attention: Doreen Morgan, Pharm D., Executive Director
Regulatory Affairs
399 Thornall Street
Edison, NJ 46285

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to your January 8, 2014 submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide multipoint dissolution profile comparison data (n=12) using the proposed QC dissolution method for the batches tested in BE studies A-U140, A-U142 (e.g. use only one unit per vessel of each strength. For example one 30 mg tablet vs. one 60 mg tablet for all the batches tested).

2. Provide multipoint dissolution profile comparisons including statistical testing (e.g. f2 similarity testing) between the 15 mg, 30 mg and 60 mg commercial batches using the QC dissolution method. The dissolution testing for each strength should be done using only one tablet per vessel (n=12).

3. Provide an explanation, as to why the coated tablets from BA study DU176b-PRT012 (b) (4) from BA study DU176-E-PRT001) (refer to Figure 1.1 section 3.2.P.5.6).

4. Submit the following data for verification of the dissolution model:
   - Step by step model development procedure, including the statistics for all the models tested (the p-values, estimated coefficients and their standard errors of the final model).
   - Raw data including both model inputs and outputs used for model development and validation.

5. Provide available data showing that the model can predict failed batches (i.e. batches that failed the dissolution acceptance criterion). This data is needed since dissolution was [redacted]% for all the batches used for model validation. In addition, the dissolution data used in the construction of the model (e.g. [redacted] are [redacted]% and there are values for which dissolution was [redacted]%. Also, evaluate the predictive power of the model by using batches that failed in vivo BE, if available.

6. In order to verify the proposed design space (e.g. same in vitro and in vivo performance) provide dissolution profiles comparisons (with statistical data) and/or in vivo data (e.g. PK data) among the batches manufactured at the extremes of the design space using the target (clinical batches) as the reference.

7. There are [redacted] listed in section 3.2.P.5.2; however, there are only [redacted] in section 3.2.P.5.2. Please clarify.

8. Provide method development information for [redacted]

9. Provide information to demonstrate that cleanliness and free of interference are maintained for [redacted].

10. You propose to perform [redacted] for the Microbial Limits test for drug product release. [redacted] If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points.

    - Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.

    - Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

    - Describe activities taken when microbiological acceptance criteria are not met at control points.

11. If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced. Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

OLEN M STEPHENS
03/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

REQUEST FOR METHODS VALIDATION MATERIALS

Daiichi Sankyo, Inc.
Attention: Doreen V. Morgan, Pharm.D.
Executive Director, Regulatory Affairs
399 Thornall street, 10th floor
Edison, NJ 08837

Dear Doreen V. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savaysa (edoxaban) tablets 15, 30 and 60 mg.

We will be performing methods validation studies on Savaysa (edoxaban) tablets 15, 30 and 60 mg, as described in NDA 206316.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

(b) (4) EDX_QB06
(b) (4) EDX_QB12
(b) (4) EDX_QB12
(b) (4) EDX_QB11
(b) (4) 400081-5, 400082-5, 400083-5
(b) (4) 400081-6, 400082-6, 400083-6
Dissolution, apparatus 2, 50 rpm UV-VIS 400081-3, 400082-3, 400083-3

Samples and Reference Standards

2 x 300 mg edoxaban tosylate drug substance reference standard
2 g edoxaban tosylate drug substance
100 Edoxaban tablets 15 mg
50 Edoxaban tablets 30 mg
50 Edoxaban tablets 60 mg
20 mg (b) (4) if available
0.5 g (b) (4) reference standard
0.5 g (b) (4) reference standard
0.5 g (b) (4) e reference standard
0.5 g (b) (4) reference standard
0.5 g (b) (4)
20 mg (b) (4) impurity if available
20 mg (b) (4) form impurity if available

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
03/06/2014

Blaus, Alison

From: Blaus, Alison
Sent: Tuesday, February 18, 2014 10:28 AM
To: Morgan, Doreen (dmorgan@dsi.com)
Cc: Golikov, Gretchen (ggolikov@dsi.com); Higgins, Janet
Subject: NDA 206316 - Clinical information Request

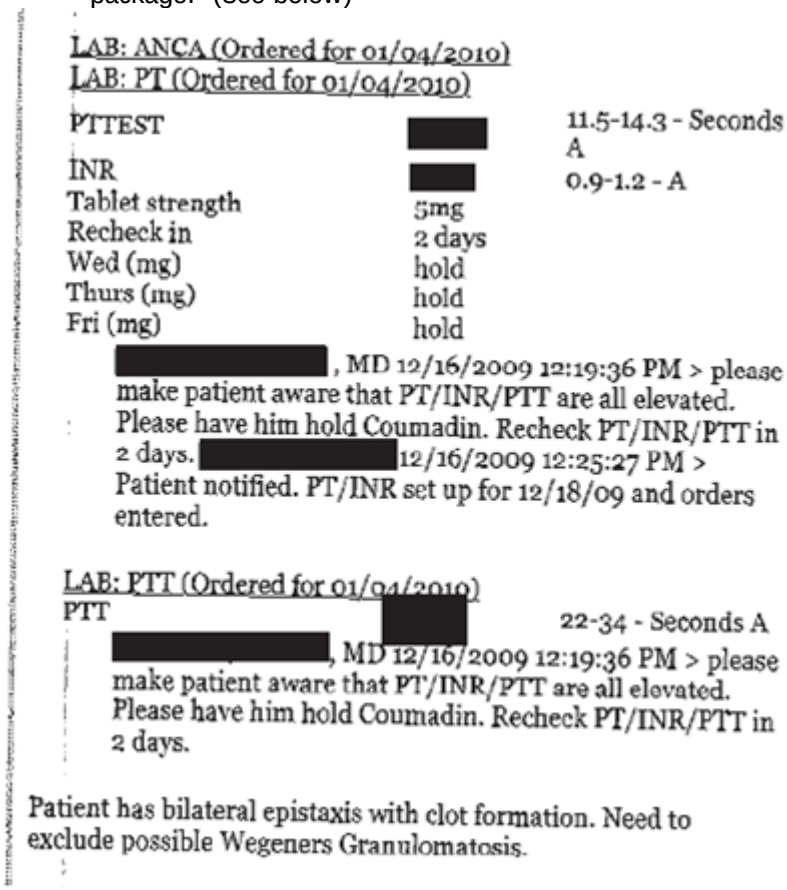
Hi Doreen –

We have two new information requests regarding two separate patients.

1. **Subject DU176b-10950003**
   According to the BLDEVCA dataset subject DU176b-10950003 had a rectal hemorrhage that was adjudicated (ADJ=1). Please confirm. If this is correct, we are unable to find the adjudication package. Please confirm it was submitted. According to the EX dataset, this subject's last dose was on 04May 2009. The BLDEVCA dataset states that the rectal hemorrhage occurred on (b) (6), so off study drug. Please explain why the variables CAONTRT, EVONTRT, and BLADJOT are "1".

2. **Subject DU176b-10950002, BLD01**
   The BLDEVCA dataset has an event date (EVSTDTC) of 2010-11-20, however the adjudication package has a date of 2009 12-25. Please explain the variable EVSTDTC that is defined as start date/time of event and why the dates aren't close.

   Please also explain why "Coumadin" appears twice in the progress notes on page 12 of 15 of the adjudication package. (See below)



LAB: ANCA (Ordered for 01/04/2010)
LAB: PT (Ordered for 01/04/2010)

PTTEST	[redacted]	11.5-14.3 - Seconds A
INR	[redacted]	0.9-1.2 - A
Tablet strength	5mg	
Recheck in	2 days	
Wed (mg)	hold	
Thurs (mg)	hold	
Fri (mg)	hold	

[redacted], MD 12/16/2009 12:19:36 PM > please make patient aware that PT/INR/PTT are all elevated. Please have him hold Coumadin. Recheck PT/INR/PTT in 2 days. [redacted] 12/16/2009 12:25:27 PM > Patient notified. PT/INR set up for 12/18/09 and orders entered.

LAB: PTT (Ordered for 01/04/2010)
PTT [redacted] 22-34 - Seconds A

[redacted], MD 12/16/2009 12:19:36 PM > please make patient aware that PT/INR/PTT are all elevated. Please have him hold Coumadin. Recheck PT/INR/PTT in 2 days.

Patient has bilateral epistaxis with clot formation. Need to exclude possible Wegeners Granulomatosis.

Thank you in advance!
Alison

Alison Blaus, RAC
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
p:(301) 796-1138
f:(301) 796-9838

Address for desk and courtesy copies:
Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4158
Silver Spring, MD 20993

Address for official submissions to your administrative file:
Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

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/s/

ALISON L BLAUS
02/18/2014

From:	Higgins, Janet
To:	Morgan, Doreen; Golikov, Gretchen (ggolikov@dsi.com)
Cc:	Blaus, Alison; Higgins, Janet
Subject:	NDA 206316 - Meeting Confirmation
Date:	Monday, February 10, 2014 10:17:26 AM
Attachments:	Foreign Visitor Form Word Template.doc NDA206313_apporient_02102014.doc

---

Dear Dr. Morgan,

Please refer to your new drug application, NDA206316/S-003 for **SAVAYSA (edoxaban tosylate) tablets.**

The application orientation presentation meeting is scheduled as follows:

Date: February 24, 2014
Time: 11:00 AM-12:00 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 2205
Silver Spring, Maryland 20903

Please e-mail me (Janet.Higgins@fda.hhs.gov) by **Friday, February 14, 2014** a list of your attendees and completed Foreign Visitor Data Request Form (attached) for each foreign visitor that will be attending the meeting . A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Janet Higgins at 240-402-0330.

Please note that I have attached some comments to assist you in preparing for your presentation, this is general advise, however, I have incorporated some comments from the team that do pertain to your application (see the statistic section of the memo) .

Sincerely,

Janet Higgins

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389

Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
02/11/2014

From:	Higgins, Janet
To:	Morgan, Doreen; Golikov, Gretchen (ggolikov@dsi.com)
Cc:	Blaus, Alison; Higgins, Janet
Subject:	Information request for NDA 206316: Edoxaban
Date:	Tuesday, February 11, 2014 7:56:48 AM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We have the following comments:

Provide study patient data listings organized by clinical site number to include the following elements below in PDF electronic format. The PATIENT DATA LISTINGS should be GROUPED and submitted to the Agency according to CLINICAL STUDY SITE (PER COUNTRY). The study subject data listings should capture the following, as applicable:
(1) subject discontinuation (If applicable per treatment group: site subject number, screening visit date, informed consent date, assent date, date of first dose/last dose, length of date of discontinuation, reason for discontinuation).
(2) prior and concomitant medications (non-study medications): (If applicable per treatment group: site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.
(3) prohibited medications (non-study medications): as above with concomitant medications
(4) adverse events, (If applicable per treatment group: preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no)).
(5) primary efficacy endpoint (recurrent venous thrombo-embolic event/s) (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1…etc).
(6) primary safety endpoint: clinically relevant bleeding (i.e., major or clinically relevant non-major bleeding) occurring during treatment or within 3 days after interrupting or stopping study drug (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1…etc).

The requested patient data listings are for the following clinical study sites:
1. Sebastian Schelling, MD, Dresden, Germany Protocol 305 Site1707
2. Barry Jacobson, M.D. Johannesberg, South Africa Protocol 305 Site 4905
3. Roger Lyons, MD, San Antonio, USA Protocol 305 Site 1002
4. Zoltan Boda MD, Protocol 305 Site 5400, Debrecen Hungary
5. Kihyuk Park MD, Protocol 305 Site 4509 Daegu, South Korea

Please respond by **February 24, 2014.**

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

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/s/

JANET G HIGGINS
02/11/2014

Blaus, Alison

From: Blaus, Alison
Sent: Sunday, February 09, 2014 10:31 AM
To: 'Morgan, Doreen'
Cc: Higgins, Janet; Golikov, Gretchen (ggolikov@dsi.com)
Subject: RE: NDA 206316 Engage FDA requested information re: adjudication Packages
Attachments: 206316 - 6Feb14 TC Information Requests .docx

Hi Doreen –

Thank you for the below. I have forwarded your preliminary response to the team. Please do submit to the NDA. Please find attached the complete list of information requests from the meeting (including expanded details about the two cases researched in the below) as well as a few additional requests that were created after our teleconference. A few of these will take time to put together, so if you need to submit piecemeal, than that is fine. Please submit via email and then follow-up with a formal submission, just to expedite matters. As mentioned in the teleconference last Thursday, we need to have these issues resolved prior to filing.

Please retain this email and attachments as formal documentation of this request.

If you have any questions, please do not hesitate to contact me.
Kind regards,
Alison

From: Morgan, Doreen [mailto:dmorgan@dsi.com]
Sent: Saturday, February 08, 2014 12:08 PM
To: Blaus, Alison
Subject: NDA 206316 Engage FDA requested information re: adjudication Packages
Importance: High

Dear Alison

It is unfortunate we did not connect yesterday, guess we were both so busy! I'm sorry for the Saturday email, but I know there is urgency on your end, so I didn't want to wait until Monday.

Please find the attached response for the Division's questions about discordance between the adjudication packages and the datasets for the two cases you provided late Thursday afternoon. With this response, we have provided documentation to support the explanatory re-adjudication activity for these cases. We propose to provide this same information for the NDA backbone through an e-submission early next week to maintain the completeness of the NDA submission contents.

Following these questions from the Division, we have further considered how best to identify if similar situations may exist in the submitted documents which could lead to additional questions about the adjudication packages. This evaluation is ongoing through the weekend – I will be able to update you next week if there are any additional findings for which advisement to the Division are required.

Please free to contact me since I can be available to speak if necessary at any time over the weekend. If nothing further this weekend, I will contact you on Monday to touch base.

Please confirm you have received this email and data, Thank you.

Regards

Doreen

Dr. Doreen V. Morgan, Pharm.D., M.S.
Executive Director
Regulatory Affairs

Daiichi Sankyo, Inc.
399 Thornall Street
Edison, NJ, 08837 USA
Phone: +1 732-590-5198
Mobile: (b) (6)
email: dmorgan@dsi.com
www. dsi.com

Passion for Innovation.
Compassion for Patients

Daiichi Action Items

Financial Disclosure

1. Please submit a new Form 3453 with a list of all investigators and sub-investigators (whether or not they signed a CRF) who disclosed no financial interests. You should list separately those who provided complete disclosure and those who provided partial disclosure. Please also provide a description of the process on how Daiichi followed up with the investigators/sub-investigators if they didn't to provide disclosure information.
2. Please confirm, via cover letter to the administrative file, that those 3 investigators (from ENGAGE – 301) listed on the Form 3455 are the only investigators that had items to disclose. If there are more investigators/sub-investigators to add to this form for any of the three studies listed, please resubmit the form.
3. Please provide a statement, in a cover letter to the administrative file, that Daiichi does not link compensation to investigators to study outcomes.

Adjudication Packages

1. Please provide an example of the cover page that you said appears at the beginning of those adjudication packages where an event was adjudicated multiple times. For example, subject DU176b-73810007 has multiple adjudications (per the ADJINV dataset), but the CRFs do not contain a cover page or bookmark indicating this.

FDA-Requested Datasets

1. Please provide pdf define files for the FDA-requested datasets.
2. Please provide the variable name for the final adjudication result.
3. Please provide the name of the SDTM dataset(s) and CRF(s) from which the ADJINV dataset (from the SDTM dataset) was created.

FDA Action Items

1. Please find the following example of a case where the adjudication package did not match the datasets:

   Example 1: Subject DU176b-73720006

   The variable CACLASS in dataset ADJINV indicates that Subject DU176b-73720006 had a non-ICH major bleed, however the adjudicators adjudicated the event as not clinically overt bleeding. The dataset does not appear to contain the adjudication results, and the dataset does not contain the individual adjudicator's information (adjudication, name and date). Please explain.

   Subject DU176b-73720006 is not found in CECDATA. Please explain why the subject does not appear in this dataset.

   The variable CACLASS in dataset BLDDATA indicates that Subject DU176b-73720006 had a non-ICH major bleed. Please explain why this differs from the adjudicator's adjudication.

   The variable TMBOFD in the dataset OVRDAT indicates that Subject DU176b-73720006 had a major bleed on Day 344. Please explain why this differs from the adjudicator's adjudication.

   Example 2: Subject DU176b-73810007, event on (b) (6)

The bleed adjudication form (BLD01) for this subject is for a cerebrovascular event (the form was not filled out). No information was found regarding the investigator's adjudication of this event. Only a "note to file" was found on page 1 of 27 that states that the event was adjudicated by Drs. Berger and Leeman on 12/23/2010 as "Intracranial bleed to be sent to Neurologists for review". These doctors are not found in the ADJINV dataset for this subject. Please explain why there was no bleed adjudication form.

The variable CACLASS in the ADJINV dataset states that the event BLD01 was adjudicated as "not a clinically overt bleed" by Drs. Silverman and Rost on 8/1/2013. Please explain why the adjudicator's assessment for this event appears to be missing. Please explain why the ADJINV dataset does not match the CRF.

The event on (b) (6) was also sent for stroke adjudication (indicated as "STR02" albeit is the first potential stroke event). The event was adjudicated as "None of the above", the variable CACLASS states "Other cerebrovascular event". The dataset CECDATA appears to match the adjudication forms, indicating that the event was adjudicated as "None of the above". However there was no bleed case report form filled out and the event was clearly an ICH. Your CA analysis dataset indicates that the event was an ICH and a major bleed, but not a stroke. Please explain the entries in the CA dataset.

Example 3: Subject DU176b-72290003, event on (b) (6)
The death was adjudicated as unrelated to a bleeding event on the adjudication form SAE02. However, the variable ADRELBLD in the ADJDTH dataset states that the bleeding contributed to death. Please explain why the dataset ADJDTH does not match the CRF. In addition, please explain why "bleeding contributed to death" was highlighted in yellow on page 3 of the adjudication form.

Post Meeting Information Requests

1. Please submit pdf define files for ALL ENGAGE data and the AF ISS data (including the "FDA" datasets). Priority should be given to ENGAGE datasets, then the AF ISS datasets. For example, with respect to the ENGAGE datasets, a pdf define file has not been submitted for the analysis files adjacrca, adjdtha, and ont3cct.
2. In your response to FDA-Requested datasets, #3, it would be helpful if you provide an annotated CRF that indicates the FDA dataset name and variables. It would be helpful if you provide this for ALL FDA requested datasets.
3. Provide a dataset that lists all subjects with one or more readjudications and the reason for each readjudication.
4. Please explain what "Note to File #44 CEC Process" means. This is found under the variable COMMENT2 in the ADJINV dataset.
5. Please explain what "(DERIVED)" means found under the variable INVCLASS. The variable is found in the BLDDATA and the ADJINV dataset. The define file indicates that INVCLASS is a TOPIC, but that is not further explained. Please define TOPIC.
6. Explain in plain language your computational algorithms found in the define files.
7. Please explain why the adjudication package for Bleed 1 for Subject DU176b-73810007 on page 17 of 27 states that the subject was on coumadin.

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/s/

ALISON L BLAUS
02/09/2014

From:	Higgins, Janet
To:	Golikov, Gretchen (ggolikov@dsi.com); Morgan, Doreen
Cc:	Higgins, Janet; Blaus, Alison
Subject:	Information request for NDA 206316: Edoxaban
Date:	Friday, February 07, 2014 7:50:15 AM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We have the following comments:

Submit as a dataset (1 site per row) the following information from clinical trial DU176b-D-U305 **by February 10, 2014**. Submit as a SAS transport file. Include a define.pdf file.

- Site number
- Principal investigator
- Location: Address, City, State, Country
- Contact Information: Name, Phone, Fax, Email
- Number of subjects screened
- Number of subjects randomized (total and per arm)
- Number of subjects treated (total and per arm)
- Number of subjects with VTE or VTE-related death (total and per arm)
- Number of subjects with major bleeding (total and per arm)
- Number of subjects with CRNM bleeding (total and per arm)
- Number of subjects with major or CRNM bleeding (total and per arm)
- Number of all-cause deaths (total and per arm)
- Number of protocol violations (total and per arm)
- Number of subjects who experienced SAEs (total and per arm)
- Number of subjects who discontinued due to AE (total and per arm)

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
02/07/2014

OSI Consult Request for Biopharmaceutical Inspections	
Date	4 February 2014
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	William H. Taylor, PhD Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division	CDER/OND/ODEI/DCRP
Project Manager	Alison Blaus, RAC
Application Type	PEPFAR? ☐ Yes ☒ No
	☒ NDA ☐ BLA ☐ ANDA
Application Number	206316
Drug Product	edoxaban
Sponsor Name	Daiichi Sankyo
Sponsor Address	399 Thornall St Edison, NJ 08837
US Agent (if applicable)	Doreen Morgan, PharmD, MS (Phone: 732-590-5198)
US Agent Address	399 Thornall St Edison, NJ 08837
Electronic Submission	☒ Yes ☐ No
PDUFA/BsUFA Due Date	8 January 2015
Action Goal Date	8 January 2015
OSI Review Requested By	Divya Menon-Andersen, Ph.D.

Inspection Request Detail (All fields should be fill out completely)				
Study #1				
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			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)
☒ Inspection Request - Clinical Site		☒ Inspection Request - Analytical Site		
Facility Name: Celerion **Address:** 1930, Heck Drive, Bldg 2, Neptune, NJ 07753.		**Facility Name:** (b) (4) **Address:** (b) (4)		
Clinical Investigator: Frank Lee, MD (email) Not available		**Principal Analytical Investigator:** (b) (4) (email) Not available		

Check one: ☒ Routine inspection ☐ For cause	Check one: ☒ Routine inspection ☐ For cause
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	
☒ Study Report: Link to document \\cdsesub1\evsprod\nda206316\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\du176b-a-u142\du176b-a-u142-body.pdf	☐ Validation Report: Link to document \\cdsesub1\evsprod\nda206316\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\07670vdac-den\07670vdac-den.pdf \\cdsesub1\evsprod\nda206316\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\080091pvkln-den-r2\080091pvkln-den-r2.pdf ☒ Bioanalytical Report: Link to document \\cdsesub1\evsprod\nda206316\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\du176b-a-u142\du176b-a-u142-ba-rpt.pdf

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

I. Appendix

Specific Items To be Addressed During the Inspection
Please contact the review division (Alison Blaus – 301-796-1138) or the clinical pharmacology reviewer (Divya Menon-Andersen – 301-796-3709) closer to the inspection date for any specific items to be addressed in the inspection.

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/s/

ALISON L BLAUS
02/04/2014

DIVYA MENON ANDERSEN
02/04/2014

RAJANIKANTH MADABUSHI
02/04/2014

From:	Higgins, Janet
To:	dmorgan@dsi.com
Cc:	Higgins, Janet; Blaus, Alison
Subject:	Information request for NDA 206316: Edoxaban
Date:	Wednesday, January 29, 2014 9:13:23 AM

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We have the following comments:

1 Provide an abbreviated data analysis of primary endpoint by geographic region for your Hokusai VTE Study.
2 Provide a rationale for assuming the applicability of foreign data in the submission to the U.S. population for treatment of VTE.

Please respond **by Monday, February 3, 2014** to NDA 206316 ORG-2 (b) (4)

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
01/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Alison Blaus, ODE 1/DCaRP, (301)796-1138

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
23 January 2014	77254 & 63266	206316	(PLEASE CHECK OFF BELOW)

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting):
edoxaban	Standard Review	NME	**8 September 2014**

NAME OF FIRM:	
Daiichi Sankyo	PDUFA Date: 8 January 2015

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
X MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:
\\CDSESUB1\EVSPROD\NDA206316\206316.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Since this NDA is a "Split Original" with (b) (4) indications being sought, please file your review to NDA 206316, but link it to Original 1, Original 2, (b) (4)

Mid-Cycle Meeting: TBD (OPDP will be invited)

Labeling Meetings: Labeling Planning Meeting not yet scheduled but OPDP will be included.

Wrap-Up Meeting: n/a

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

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/s/

ALISON L BLAUS
01/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: OSE	Alison Blaus, ODE 1/DCaRP, (301)796-1138

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
23 Jan 2014	77254 & 63266	206316	NDA Submission	8 Jan 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
edoxaban	Standard NDA Review	NME	8 September 2014

NAME OF FIRM: Daiichi Sankyo

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Carton/Container Labels

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review these carton/container labels for this NDA, cangrelor.
Link to the Application
\\CDSESUB1\EVSPROD\NDA206316\206316.enx

Since this NDA is a "Split Original" with (b) (4) indications being sought, please file your review to NDA 206316, but link it to Original 1, Original 2, (b) (4)

PDUFA DATE: 8 January 2015

ATTACHMENTS: Draft Package Insert, Container and Carton Labels (please see these documents at the above EDR location.

CC: Archival IND/NDA 206316
.FD-110/Division File
HFD-110/RPM
HFD-110/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER Alison Blaus	METHOD OF DELIVERY (Check one) ☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

ALISON L BLAUS
01/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Karl Lin, Team Leader, Division of Biometrics 6 (Applications in Pharmacology / Toxicology)	ALISON L. BLAUS, ODE 1/DCaRP, (301) 796-1138

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
22 January 2014	77254	206316	NDA original submission with results of CARC studies	8 January 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Savaysa™ (edoxaban) (Drug code: DU-176b)	Standard NDA	Anticoagulant agent (Factor Xa inhibitor)	30 May 2014

NAME OF FIRM: Daiichi Sankyo, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☒ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: We are requesting a nonclinical statistical review of the carcinogenicity data for Savaysa™ (edoxaban), tablets for oral use. There are two CARC studies - AN07-C0019-R01 in CD mice (104 weeks), and AN20-C0020-R01 (please also see a report AN11-H7301-R01) in SD rats (104 weeks). The submission, including dataset, is located in DARRTS, NDA 206316, SD 1, eCTD seqno 0000, dated 1/8/2014, module 4.2.3.4.

Link to the Application
\\CDSESUB1\EVSPROD\NDA206316\206316.enx

Please include in your review the following questions, and any other issues you think should be addressed:
1) whether there is any difference in survival (or death) among groups; if yes, whether the difference is statistically significant; 2) whether there is any difference in incidences of any neoplastic finding among groups, if yes, whether the difference is statistically significant.

Since this NDA is a "Split Original" with (b) (4) indications being sought, please file your review to NDA 206316, but link it to Original 1, Original 2, (b) (4)

The Pharmacology/Toxicology reviewer for this NDA is Baichun Yang. Please notify Baichun, Thomas Papoian, and me of the name of the statistician assigned to this consult request. This data will need to be taken to Exec CAC in June 2014. Therefore, we want to have both the Pharm/Tox and Statistical Consult Review completed at least 10 days prior to the Exec CAC meeting, so we can incorporate the Statistical Consult Review into our Final Pharm/Tox review before the date of the Exec CAC meeting. If you have any questions, please do not hesitate to contact Baichun, Tom, or me. Thank you in advance!

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
ALISON L. BLAUS	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

ALISON L BLAUS
01/22/2014

BAICHUN YANG
01/22/2014

THOMAS PAPOIAN
01/22/2014
Concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1
NDA 206316/Original 2
(b) (4)

NDA ACKNOWLEDGMENT

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets

Date of Application: 8 January 2014

Date of Receipt: 8 January 2014

Our Reference Number: NDA 206316

NDA 206316 provides for the use of SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets for the following indications which, for administrative purposes, we have designated 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)

NDA 206316/Original 1 will be reviewed by the Division of Cardiovascular & Renal Products and NDA 206316/Originals 2 (b) (4) will be reviewed by the Division of Hematology Products.

All future submissions to your NDA should specify the NDA number and all Original numbers to which each submission pertains.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 9, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number and all pertinent Original numbers provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular & Renal Products **or**
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call the following Regulatory Project Managers:

For NDA 206316/Original 1 – Alison Blaus, RAC at (301) 796-1138
For NDA 206316/Original 2 – Janet Higgins at (240) 402-0330
(b) (4)

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
01/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 63266

MEETING MINUTES

Daiichi Sankyo, Inc.
Attention: Gretchen Golikov
Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Ms. Golikov:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Edoxaban (DU-176b) tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2013. The purpose of the meeting was to review top-line results from the Hokusai VTE study and confirm the acceptability of the pivotal study data to support NDA filing of Edoxaban Tosylate (DU-176b) Tablets, Savaysa™.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janet G. Higgins, Regulatory Project Manager at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 18, 2013; 10:00AM to 11:00 AM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 63266
Product Name:	Edoxaban (DU-176b) tablets
Indication:	For the treatment of DVT, PE (b) (4)
Sponsor/Applicant Name:	Daiichi Sankyo, Inc.
Meeting Chair:	Dr. Kathy Robie-Suh
Meeting Recorder:	Janet G. Higgins

FDA ATTENDEES

Division of Hematology Products (DHP)

Ann T. Farrell, M.D., Director
Edvardas Kaminskas, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Medical Officer, Clinical Team Leader, Hematology
George Shashaty, M.D., Medical Officer
Alexandria Schwarsin, Medical Officer
Lara Akinsanya, M.S., Senior Regulatory Project Manager
Diane Leaman, Safety Regulatory Project Manager
Janet G. Higgins, Regulatory Project Manager

Division of Hematology Oncology Toxicology
Brenda Gehrke, Ph.D., Pharmacologist

Division of Clinical Pharmacology V
Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader

Division of Biometrics V
Qing Xu, Ph.D., Biostatistics Reviewer
Lei Nie, Ph.D., Biostatistics Team Leader

Division of New Drug Quality Assessment I
Janice Brown, M.S, CMC Lead
Anne Marie Russell, Ph.D., Product Quality Reviewer

Division of Cardiovascular and Renal Products
Alison Blaus, Regulatory Project Manager

Office of Pharmacovigilance and Epidemiology
John R. Senior, M.D., Associate Director for Science
Ted Guo, Mathematical Statistician

Office of Planning and Informatics
Kimberly Taylor, Operations Research Analyst

SPONSOR ATTENDEES

Mahmoud Ghazzi, MD, Executive Vice President & Chief Medical Advisor
Michele Mercuri, MD, PhD, FAHA, Vice President, Clinical Development
Michael Grosso, MD, Senior Director, Clinical Development
Kimberley Stranick, MS, PhD, Vice President, Regulatory Affairs
Doreen Morgan, PharmD, MS, Executive Director, Regulatory Affairs
Gretchen Golikov, Director, Regulatory Affairs
Tetsuya Kimura, MS, RPh, Senior Director, Japan Clinical Development
Youngsook Choi, MD Senior Director, Clinical Safety and Pharmacovigilance
Karen Brown, PhD, Executive Director, Clinical Pharmacology
Minggao Shi, PhD, Senior Director, Biostatistics

Consultants:

(b) (4)

(b) (4) Associate Director, Biostatistics, (b) (4)

Eastern Research Group (Independent Assessor)

Patrick Zhou

1.0 BACKGROUND

The purpose of this type B pre-NDA Meeting is to review top-line results from The Hokusai VTE study and confirm the acceptability of the pivotal study data to support NDA filing of Edoxaban Tosylate (DU-176b) Tablets, Savaysa™. The majority of the inquiries are focused on the format and content for the clinical study report and the submission of the NDA were discussed at the Type C Meeting on November 13, 2012.

The single pivotal study for the indication of the treatment of DVT and PE (b) (4) is titled DU176b-D-U305 "A Phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for the evaluation of efficacy and safety of (low Molecular Weight-LMW) heparin/edoxaban versus (LMW) heparin/warfarin in subjects with symptomatic deep-vein thrombosis and/or pulmonary embolism(Hokusai VTE)".

2. DISCUSSION

2.1. Sponsor Questions/FDA Responses

Question 1: Does the Division continue to concur with the agreements reached at the Type C meeting on November 13, 2012?

FDA Response to Question 1: **The agreements reached at the Type C meeting on November 13, 2012 as reflected in the Meeting Minutes remain valid.**

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 2: Does the Agency concur that submitting a single eCTD to include two indications as described is acceptable?

FDA Response to Question 2: **The submission of a single eCTD to include different indications is acceptable provided that there is a clear separation in the submission for each indication. Documents related to the VTE indication should be clearly separated from the documents for the AF indication. Documents that are common to both indications should be clearly delineated. Since some documents may be overlapping but not identical for the different indications (e.g., Clinical Overview), some system should be employed to ensure that each document in the submission has a unique identifier. The identifier may need to be carried through the pagination of some documents to ensure that they are easily associated with the proper indication.**

FDA's guidance for industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (bundling policy) describes FDA's current thinking on what should be contained in separate marketing applications and what

should be combined into one application for the purposes of assessing user fees. Generally, the bundling policy states that every different active ingredient or combination of active ingredients, different route of administration, and different dosage forms should be submitted in different original applications. It also states that for products which differ in excipients that require separate clinical studies of safety or effectiveness (because of the differences in excipients) should not be submitted in the same original application. The bundling policy also states that if submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration can be regarded, for the purposes of assessing user fees as one application. We concur that a single application with two indications is acceptable as long as the two indications are submitted simultaneously in one application as your proposed products (i.e., the 15, 30, and 60 mg tablets) have the same active ingredient, they are the same dosage form, and have the same route of administration. Because we believe you meet the conditions for the submission of one application, then we would also expect one user fee. We would expect a full user fee for an application that requires clinical data for approval. Please note that the full fee for an application that requires clinical data for approval for fiscal year 2014 (from Oct 1, 2013 through September 31, 2014) is $2,169,100. Further, questions regarding user fees and/or bundling issues can be addressed to Michael Jones, CDER's Office of Management (phone 301-796-7900).

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 3: Does the Division believe proposed REMS is a required component of this NDA for Savaysa™? If a REMS is required because the Division believes it is necessary to ensure that the benefits of Savaysa™ outweigh the risks, can this component of the NDA be submitted within 30 days of the initial NDA filing as allowed by PDUFA V?

FDA Response to Question 3: **At this time, we do not foresee a need for risk evaluation and mitigation strategies (REMS). If upon review of the data in your submission we see a need for REMS, it is acceptable for a REMS proposal to be submitted during the course of the FDA review as the evidence indicates.**

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 4: Is the DS understanding of the eDISH information required correct?

FDA Response to Question 4: **Please note the following specifications of Clinical Narrative Data for eDISH:**

- **Narrative data as a SAS data set**

1. **STUDYID (Required): Unique identifier for a study within the submission (Char)**
2. **USUBJID (Required): Unique subject identifier within the submission (Char)**
3. **NARRATIVE* (Required): Clinical Narrative (Char)**

   ***: *Requirements for Variable NARRATIVE - To the medical writer*:**

   Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hy's Law" cases of elevated ALT or AST >3xULN and TBL >2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings. This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug- related liver injury (DILI) be made. Liver biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL >2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH system, as used by medical reviewers at CDER, includes the capability to create time-course graphs for each subject, and to read the narrative summaries, helping them in drawing their own conclusions as to whether the drug may have caused the abnormal findings. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

   Therefore, we recommend that the narratives should be written by physicians or other medical personnel skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

   It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives for subjects with either ALT > 5xULN or TBL > 2xULN. The narratives should include information described in the following points:

   1. **Indication**
   2. **Subject's medical history and concomitant medications**

3. **Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy**
4. **Time course of any signs or symptoms of liver disease, including jaundice**
5. **Differential diagnosis and final diagnosis of liver disease**
6. **The study site investigator and the sponsor's assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events**
7. **Clinical course of liver-related adverse events including treatment and outcome**
8. **Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation.**
9. **It is also helpful to include in the narrative:**
    a. **Dose and duration of study therapy in weeks**
    b. **Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements**

- **<u>The Supplemental Narrative data as PDF files</u>**

Format of Supplemental Narratives in PDF

When the sponsor submits the clinical narratives in a SAS data set, it should be allowed to supplement narratives in PDF files. Such flexibility should add more power to eDISH in determining potential DILI.

***The supplemental narratives can be submitted in the following fashion*:**

1. **Each supplemental PDF file only represents one subject of interest. The name of the PDF file is the unique subject ID: USUBJID that is used in the data submission to the FDA.**
2. **No two subjects should share the same PDF file.**

The supplemental narratives may include any forms of text, bullet points, tables, graphs, or other eye-catching tools that PDF format permits. However, they should be kept simple, clear, and informative.

***Important Note for Sponsor's data manager*:**

Due to limitations and restriction of the FDA gateway system, the narratives submitted through the FDA gateway system could be truncated. To ensure the FDA reviewer receive complete narratives, please burn the narratives (as SAS data set) and the optional/supplemental narratives on a CD/DVD, and then mail to the review division as a desk copy to compensate such limitations.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 5: Does the Agency foresee that the proposed NDA will be reviewed by the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)? If so, can the Agency comment on the timing of a CRDAC review or the earliest time point in the review cycle that the Sponsor will be notified?

FDA Response to Question 5: **Whether Edoxaban will be discussed at an advisory committee meeting is a review issue and will be determined after the application is submitted.**

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 6: Does the Agency concur with the proposed timing for a Safety Update?

FDA Response to Question 6: **Yes, we agree.**

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

2.2. Hokusai VTE Data Summary

Question 7: Based on the results of Hokusai VTE, DS believes we qualify for a Priority Review Designation for the NDA; does the Division concur?

FDA Response to Question 7: **You may request a priority review for your NDA if you believe that the data support such a review. A decision for a priority review will be made after receipt of a submission requesting a priority review. Because of the availability of a number of agents for the indications proposed, it is not likely that a priority review would be granted.**

Discussion:

The sponsor explained their argument for priority review is based on results in certain subpopulations in the study (e.g. cancer patients). The agency commented that the sponsor should make their argument for priority review in the NDA submission.

Question 8: The primary efficacy endpoint was achieved and demonstrated consistency across multiple data sets and analyses. Does the Agency concur that this is adequate to support the following indication in the label?

(b) (4)

FDA Response to Question 8: **The report of the VTE Data Summary under Tab 6 of the submission is noted. The adequacy of the data to support the proposed indications is a review issue.**

Discussion:

Discussion regarding the wording of the proposed indication took place. The Agency commented that the final wording of the indication is a review issue dependent on study results and is influenced by how the study was done.

Question 9: Does the Division concur that the Savaysa™ 30 mg dose administered to subjects with low body weight, reduced creatinine clearance and concomitant use of protocol pre specified P glycoprotein inhibitors is effective and safe comparable to the Savaysa™ 60 mg dose?

FDA Response to Question 9:

Your general approach to dose modify based on exposure matching using presumed changes in exposure from dedicated intrinsic and extrinsic factor trials appears reasonable. The final determination regarding the adequacy of your proposed 30 mg dose modification will be a review issue. A comprehensive justification of your proposal, across all relevant in vitro studies and clinical trials, should be prominently included in your clinical pharmacology summary.

Discussion:

In discussion it was emphasized that this is a review issue.

2.3. Additional Comments

Clinical Pharmacology:

Regarding clinical pharmacology related information in your planned application please consider the following:

- In your clinical pharmacology summary please include a comprehensive evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK and PD of your drug that spans all approved and proposed indications.
- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.
- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation, arithmetic mean ± standard deviation, and median with range where appropriate.
- We encourage you to refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm). For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Division of Medication Error Prevention and Analysis (DMEPA) Comments

- Please submit a request for the proposed proprietary name for re-evaluation of Savaysa at the time of NDA submission.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  A complete NDA packet should contain relevant information to permit the FDA reviewers to reach the following key decisions:

  - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
  - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

  The documentation required in an NDA is supposed to tell the drug's history, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged. The following link provides summaries on NDA content, format, and classification, plus the NDA review process: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held and it was concluded that at this time, we do not foresee a need for risk evaluation and mitigation strategies (REMS). If upon review of the data in your submission we see a need for REMS, it is acceptable for a REMS proposal to be submitted during the course of the FDA review as the evidence indicates.

In addition, we note that a chemistry pre-submission meeting was held on May 17, 2013. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the discussion.

6.0 ATTACHMENTS AND HANDOUTS

Please refer to the presentation slides that were provided by the sponsor.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

KATHY M ROBIE SUH
09/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 63266 and IND 77254

MEETING MINUTES

Daiichi Sankyo, Inc.
Attention: Linda Nelson, PhD
Director, Regulatory Affairs, CMC
399 Thornall Street
Edison, NJ 08837

Dear Dr. Nelson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Edoxaban (DU-176b) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 17, 2013. The purpose of the meeting was to discuss specific CMC topics and provide overviews of the strategies that will be incorporated to support the registration of the Edoxaban NDA and to ensure that Diiachi Sanyko incorporates FDA comments from both branches in their development plans.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment
Food and Drug Administration

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA, CMC
Meeting Date and Time:	May 17, 2013, 9:00AM-10:30AM (EST)
Meeting Location:	White Oak Building 22, Conference Room: 1419
Application Number:	IND 63266 and IND 77254
Product Name:	Edoxaban (DU-176b) Tablets
Indication:	Treatment of (b) (4) venous thromboembolism (VTE) and (b) (4) pulmonary embolism
Sponsor/Applicant Name:	Daiichi Sankyo, Inc.
Meeting Chair:	Ali Al Hakim, PhD
Meeting Recorder:	Jewell Martin, MA, MBA, PMP Teshara Bouie, MS

FDA ATTENDEES

Office of New Drug Quality Assessment:
Ali Al Hakim, PhD, Branch Chief
Ramesh Sood, PhD, Branch Chief
Hasmukh Patel, PhD, Post Marketing Branch Chief
Janice Brown, MS, CMC Lead
Sandra Suarez Sharp, PhD, Biopharmaceutics Reviewer
Sharmista Chatterjee, PhD, QbD Lead
Bogdan Kurtyka, PhD, QbD Reviewer
Anne Marie Russell, PhD, Chemistry Reviewer
Zedong Dong, PhD, Chemistry Reviewer
Christine Moore, PhD, Acting Director Office of New Drug Quality Assessment
Yvonne Knight, MS, Regulatory Project Manager for Quality
Teshara G. Bouie, MS, Regulatory Project Manager for Quality
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager for Quality

Office of Manufacturing and Product Quality
Vipul Dholakia, PhD, Interdisciplinary Scientist - Chemist
Mahesh Ramanadham, Pharm D, Regulatory
David Doleski, PhD, Division Director, Division of Good Manufacturing Practice Assessment
Seongeun (Julia) Cho, PhD, (Acting) Branch Chief, New Drug Manufacturing Assessment

Division of Cardio-Renal Products:
Patricia Harlow, PhD, Pharmacology Reviewer

Division of Hematology Products:
George Shashaty, MD Medical Officer

Division of Hematology, Oncology, Toxicology:
Brenda Gehrke, PhD, Pharmacology Reviewer
Haleh Saber, PhD, Supervisory Pharmacologist

SPONSOR ATTENDEES
Daiichi Sankyo Pharma Development:
George Chen, Ph.D, Executive Director, US Regulatory Affairs-CMC
Linda Nelson, Ph.D, Director, Regulatory Affairs-CMC
Motonori Kidokoro, Ph.D, Director, Regulatory Affairs-CMC
Jack Rosen, Director, Pharmaceutical Development

Daiichi Sankyo Co., Ltd.:
Koutaro Kawanami, Sr. Researcher, Process Technology Research Laboratories
Tomoyuki Watanabe, Ph.D, Sr. Director, Formulation Technology Research Laboratories
Hiroshi Nakagawa, Associate Sr. Researcher, Formulation Technology Research Laboratories
Tadanobu Takatani, Senior Researcher, Analytical and Quality Evaluation Research Laboratories
Hiroki Hifumi, Ph.D, Researcher, Analytical and Quality Evaluation Research Laboratories
Kenichi Enokita, Associate Director, CM&C Planning Department
Hiroyuki Nakata, Associate Director, CM&C Planning Department

1.0 BACKGROUND

On February 4, 2013, the FDA received correspondence from Daiichi Sankyo, Inc. requesting a Type B meeting to discuss specific CMC topics and provide overviews of the strategies that will be incorporated to support the registration of the Edoxaban NDA and to ensure that Diiachi Sanyko incorporates FDA comments from both branches in their development plans. The FDA accepted the request and issued a Meeting Granted letter on February 14, 2013. The meeting package was received March 20, 2013.

The face to face meeting with Daiichi Sankyo, Inc. was initially scheduled to occur on April 17, 2013. After reviewing the meeting package, the FDA determined that additional expertise was necessary. After discussion with the sponsor, the meeting date was changed to May 17, 2013, in order to accommodate scheduling for Daiichi Sankyo, Inc. meeting participants and FDA meeting participants.

The FDA's Preliminary Comments were sent to Daiichi Sankyo on May 13, 2013. After reviewing the comments, Daiichi Sankyo proposed to discuss the following items:

Topic	Reference in FDA Letter	Estimated Time
(b) (4) Based Design Space	Q6a	25 minutes
Relationship of Design Space (b) (4)	Q6b(i)	
(b) (4)	Q8 a(ii)	
(b) (4) Starting Material	Q1	20 minutes
Control Strategy for Genotoxic Impurities	Q2c	
Dissolution Model Updates	Q5c (ii)	25 minutes
Dissolution Acceptance Criteria for (b) (4)	Q6b(i)	
Sampling Plans	Q6a(iv)	If sufficient time is available
Decision Trees	Q7a(iv)	
Validation Criteria for Dissolution Model	Q8b	
Chiral Identification Test and (b) (4)	Q2a (i and iii)	
(b) (4) Batch Release	Q2d(ii)	
Post-approval annual batch stability protocol	Q4(iii)	

2.0 DISCUSSION

Question 1:
Does the revision of the specifications for (b) (4) starting material satisfy the recommendations made by the Agency at the EOP 2 meeting? Specifically, is Daiichi Sankyo's approach to setting the acceptance criteria for related substances and residual solvents based on spike and recovery experiments acceptable to the Agency?

FDA response to Question 1:
(b) (4)

it is recommended that it be designated (b) (4) **as proposed.** (b) (4)

Daiichi Sankyo Response sent on 5/16/2013:
See Appendices for Slides – Question 1: (b) (4) (Slides 29-36)

Meeting Discussion:
The sponsor intends to submit additional information in the NDA to support the use of this starting material. The FDA stated that the information submitted in the meeting package does not support the use of (b) (4) as a starting material.

The FDA stated that the sponsor's justification should be based on Q11 guidance.

The FDA will have additional discussion and provide post meeting feedback and add as an addendum to the meeting minutes. FDA will discuss what additional information, if any, that Daiichi should provide in the NDA to support their proposal.

See Post Meeting Feed Back (Section 3.0) for additional comments from the FDA.

Question 2:

2a. Does the Agency agree with the completeness and acceptability of tests proposed for edoxaban tosylate drug substance release?

FDA response to Question 2a:

Insufficient information is provided at this time to determine acceptability of the proposed (b) (4) This will be a review issue. Find below some additional comments for your consideration:

i. **Include an (b) (4) method.**
ii. **Expand the (b) (4) or justify their exclusion with data.**
iii. **Include a test for the (b) (4) or justify its' exclusion with data.**

Meeting Discussion:

Due to time constraints topic was not discussed.

2b. Does the Agency agree with the proposed control strategy for (b) (4) impurities where testing for these compounds will not be performed on edoxaban tosylate drug substance? Further, is the proposed data set outlined above sufficient to support the proposed control strategy?

FDA response to Question 2b:

The proposed control strategy for (b) (4) impurities appears to be acceptable, but the final assessment will be a review issue. Of particular concern are the in-process controls for (b) (4)

Meeting Discussion:

No further discussion required.

2c. Does the Agency agree with the proposed control strategy for known genotoxic impurities (GTIs) that are controlled in the individual starting materials, specifically (b) (4) and (b) (4), and not in the final drug substance? Further, is the proposed data set outlined below sufficient to support the proposed control strategy?

FDA response to Question 2c:

No. The proposed control strategy does not include (b) (4) and relies solely on (b) (4) For the risk associated with (b) (4) would be expected unless otherwise justified.

For the evaluation of the potential genotoxic impurities using (b) (4), it is recommended that two different SAR prediction methods be applied, such as an expert rule-based and a statistical-based model. It appears that you only used DEREK, i.e. an expert rule-based approach. A statistical-based model should be used in addition to DEREK. Please submit the SAR analyses for our review in the NDA; include the version of DEREK used. Your decision to strictly control (b) (4) as a potential genotoxic impurity based on the positive result in DEREK is acceptable.

The proposed acceptance criteria for the genotoxic impurities (b) (4) in (b) (4) of NMT (b) (4)% are expected to result in levels (b) (4)ppm (the limit of quantitation) in the edoxaban drug substance. Based on the information rovided and the summary tables of your spike/recovery studies, the acceptance criteria for genotoxic impurities (b) (4) (b) (4) ppm for the maximum dose of 60 mg/day are acceptable.

Daiichi Sankyo Response sent on 5/16/2013:

See Appendices for Slides - Question 2c: GTI (Slide 37-38)

Meeting Discussion:

The FDA stated that if DEREK does not result in a positive response (referred to as a "no call"), it should not be concluded that the impurity is non-genotoxic. The FDA discussed different options when DEREK results in "no call", i.e. to use a statistical-based approach in addition to DEREK, to conduct Ames in addition to DEREK (as proposed by the Sponsor), or alternatively just conduct the AMES assay if the Sponsor chooses not to use any SAR approach.

2d. Does the Agency agree with the control strategy for genotoxic impurities arising during (b) (4) edoxaban tosylate? Further, is the proposed data set outlined sufficient to support the proposed control strategy? Finally, does the Agency agree that a comparability protocol and CBE-30 supplement may be submitted (b) (4)

FDA response to Question 2d:

i. **Regarding control strategy – this may acceptable provided sufficient supportive data is provided. The final assessment will be a review issue.**
ii. **Regarding the data set – release batch data for (b) (4) may be indicated to support its' exclusion from release specifications.**
iii. **No, we do not agree with your proposal of submitting a comparability protocol and CBE-30 supplement (b) (4) We recommend that you submit a prior approval supplement with data to support (b) (4)**

iv. **Regarding the genotoxic impurities [redacted] that arise from [redacted] edoxaban tosylate, the proposed acceptance criteria of NMT [redacted] ppm for the total of all three impurities is acceptable based on the [redacted] ppm for the maximum dose of 60 mg/day.**

Meeting Discussion:
Due to time constraints topic was not discussed.

Question 3:
Does the Agency agree that the data package for the primary registration stability manufactured at [redacted] is adequate to establish a retest period for the drug substance manufactured at the [redacted] commercial site, if equivalence is shown with 9 months site-specific stability data for three lots from full-scale commercial manufacturing at [redacted]?

FDA response to Question 3:
Yes. The retest period will be a NDA review issue.

Meeting Discussion:
No further discussion required.

Question 4:
Does the Agency agree that the current stability program, consistent with ICH Q1A, Q1B and Q1D, and that the validation protocol and post-approval annual batch protocols are acceptable?

FDA response to Question 4:

i. **Regarding current stability program for drug product – the meeting package indicated that the proposed primary stability batches (tablets) were manufactured at pilot scale ([redacted] of the commercial) with two lots of clinical drug substance [redacted]) packaged in the to-be-marketed configuration. Eighteen to twenty four months of long-term stability data will be submitted in the NDA. This proposal may be acceptable provided the primary stability batches were manufactured using the commercial process.**

ii. **Regarding the stability protocol: [redacted] proposals are included in the meeting package (Option 1 Table 5.4.7 and Option 2 Table 5.4.8) - Option 1 does not include [redacted] Option 2 includes the 7 ct bottle presentation and omits 30mg (mid-strength) tablets in all packaging presentations plus the 30 ct bottle at all three strengths. This design appears to be consistent with Q1D and may be acceptable provided the stability data of the extremes in the bracketing design are comparable, which will be a review issue.**

iii. **Regarding the post-approval protocol: The annual batch stability protocol should also include 3, 6, 9, and 18 months time points. The [redacted] proposal [redacted]**

[redacted] **Please note this design is unacceptable. A similar design as Option 2 (Table 5.4.8 in the submission) is scientifically more reasonable and the 7 count bottle should be included.**

Meeting Discussion:
Due to time constraints topic was not discussed.

Question 5:

5a. Does the Agency agree with the completeness of the list of tests proposed for edoxaban drug product release and stability? Specifically, the [redacted] will not be performed [redacted] per the agreement reached with the Agency at the Type "C" meeting to allow for [redacted]

FDA response Question 5a:

Your proposal to include a rationale in the NDA to support your proposal to [redacted] appears to be reasonable. However, insufficient information is provided at this time to assess the acceptability of [redacted] as proposed. This will be a review issue.

Additional comments:

i. **Justify the proposal to [redacted] on release and stability by data.**
ii. **Your proposal to notify updates about [redacted] (refer footnote (a) of table 5.5.2) is not adequate. These models are regarded as high impact models, [redacted] are sole indicators of bioavailability of the finished product. Hence, changes to these models have a potential to adversely affect product quality and should be notified to the FDA in accordance with 21 CFR 314.70.**

Daiichi Sankyo Response sent on 5/16/2013:
See Appendices for Slides - Topic 5a (ii): Update of Dissolution Model (Slides 39-41)

Meeting Discussion:
The FDA viewed the dissolution models as high risk/impact models. The FDA asked the sponsor to provide a high level summary of model maintenance approach in the NDA submission and clarified that it is the FDA's expectation that details regarding model maintenance would be available on site for review during inspections. The FDA suggested the sponsor refer to the section on Models in ICH Points to Consider document.

The sponsor stated that [redacted] were measured [redacted]

The FDA referred the Sponsor to slides number 41 and 48 presented during the meeting and stated that the relationships reported between percent dissolution, particle size and tablet density are unusual. The FDA inquired about an explanation/justification for why a [redacted]

[redacted] The sponsor stated that they were also surprised when they first saw the data, but that they will provide additional data and a detailed explanation of these observations.

5b. Does the Agency agree with the format of the proposed specifications for [redacted]

FDA response to Question 5b:

It is suggested to combine Tables 5.5.1 [redacted] into a single table indicating which analytical tests would be applicable for [redacted] respectively. Also indicate the methods that will be used for routine commercial production and those that are alternate. Additionally, since values for [redacted], include values of these [redacted] on the specification sheet, indicating that these are [redacted] Note that Table 5.5.2 [redacted] which should be included regardless of which [redacted]

We noticed that the calculation you propose for uniformity of dosage units is based on [redacted] and uses [redacted] acceptance limit. However, while the [redacted] method is based on measuring the active content of individual tablets, your proposed procedure relies on an [redacted] As indicated during the 2010 face to face meeting, the FDA perceives that there is a risk due to [redacted], and we recommend that in addition to the data provided in the meeting package (e.g. table 5.6.7 and Fig 5.6.19), you provide data from commercial scale batches showing a one on one comparison of active content of individual tablets measured by the traditional method (e.g. HPLC) versus your method , for a statistically significant number of tablets from each batch.

Furthermore, our simulation indicates that your proposed procedure yields results of acceptance values for [redacted] on the same input values. You should re-evaluate and justify the acceptance limit.

Meeting Discussion:

The sponsor asked about details of simulations mentioned in the response. The FDA stated that [redacted] and approach proposed by the sponsor. The calculation was performed in Excel.

5c. Does the Agency agree with the approach to setting the dissolution acceptance criteria for [redacted] as Q= [redacted]% and [redacted] as not less than [redacted]%?

FDA response to Question 5c:

1. **Your approach for setting the dissolution acceptance criterion (b) (4) is not acceptable. Note that since the acceptance criterion for (b) (4) is based on the acceptability of the criterion (b) (4), it is also not acceptable.**
2. **The acceptance criterion (b) (4) should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12). Data from the bio-batches (pivotal phase 3 & PK) and registration stability batches should be used for the setting of the dissolution acceptance criterion.**
3. **Also, there is not sufficient information to make a recommendation on an adequate dissolution acceptance criterion. A preliminary evaluation indicates that a criterion of Q= (b) (4)% at (b) (4)min might be more appropriate for your product and will improve the discriminating capability of the method. Provide the following information:**
    a. **Complete dissolution profile data (raw data and mean values) from the pivotal Phase 3 clinical and registration batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.**
    b. **Individual and mean values in tabulated form and graphical form (mean values) for all the batches listed in Table 5.5.6.**
    c. **Data demonstrating that the proposed dissolution acceptance criterion is able to reject batches outside the ranges of your proposed design space (e.g. drug products that are intentionally manufactured with meaningful variations, i.e., ± (b) (4)% change to the specification-ranges) for the most critical manufacturing variables (e.g. (b) (4) etc.)**
    d. **If available, submit data showing the capability of the selected dissolution method/acceptance criterion to reject batches that are not bioequivalent.**
    e. **Provide data demonstrating the discriminating ability of the dissolution method to detect the presence of the most relevant (b) (4) in the drug product. Include a complete assessment of the apparent pH dependent solubility, inherent dissolution rate, the ability of the proposed dissolution method to screen for (b) (4) in the drug product and a discussion (with supporting data) on the clinical impact of (b) (4)**
    f. **The criterion for the (b) (4) should be based on passing the acceptance criterion based not only on mean values but also when both the minimum and maximum values for each variable are incorporated in the model.**

Daiichi Sankyo Response sent on 5/16/2013:

See Appendices for Slides - Topic 5c (i): Dissolution Acceptance Criteria (Slides 42-52)

Meeting Discussion (Q5c 1):
The Sponsor inquired regarding further clarification as to why the [redacted] (b) (4) is not acceptable for establishing the dissolution acceptance criterion. The FDA stated that the reason why the [redacted] (b) (4) is not acceptable is because [redacted] (b) (4)

The FDA added that dissolution acceptance criteria is established based on average in vitro dissolution data for each lot under study (such as pivotal phase 3 and stability batches, excluding accelerated stability data), equivalent to USP Stage 2 testing (n=12) (refer to IVIVC guidance for industry). More permissive /wider acceptance criterion can often be justified with in vivo data (e.g., BA/BE data). The sponsor mentioned that edoxaban is a BCS Class 4 and an immediate release compound for which an IVIVC is not possible. The FDA responded that the review team was not asking to establish a correlation, but to determine the relationship between variations in any [redacted] (b) (4) in vitro dissolution and systemic exposure (e.g. Cmax and AUC).

The sponsor added that the FDA previously agreed to setting a dissolution acceptance criterion of Q= [redacted] (b) (4) % at 30 min. The FDA responded that it was clearly stated in the communication given back i 2010 that the recommended acceptance criterion was preliminary and that it could change as more data is presented. As stated in the preliminary written comments, the data submitted in the current meeting package support an acceptance criterion of Q= [redacted] (b) (4) % at [redacted] (b) (4) min, specially for the lower strengths. However, this current recommendation is still preliminary pending scientific justification supporting the opposite trends in the relationship observed between dissolution and the [redacted] (b) (4) Also, a wider acceptance criterion could be accepted if in vivo BE data is provided supporting it.

The FDA stated that Q = [redacted] (b) (4) % is acceptable, however, the FDA does not agree with the sampling time.

See Post Meeting Feed Back (Section 3.0) for additional comments from the FDA.

Question 6:
Based on Daiichi Sankyo's understanding of the recommendations, listed above, provided by the Agency at the Type "C" meeting, Daiichi Sankyo seeks concurrence with the approaches taken to address the Agency's recommendations.

6a. Does the Agency agree that the refinements made to the QbD program address the previous Agency comments and that the proposed [redacted] (b) (4) ?

FDA response Question 6a:
The information submitted does appear to respond to some previous FDA comments regarding the QbD program (e.g. [redacted] (b) (4)

Regarding the proposed (b) (4) based design space, the FDA views your strategy of monitoring (b) (4) The FDA would like to remind you to define design space in concurrence with ICH Q8 (R2) in terms of input parameters not output parameters e.g. (b) (4). Since some processes e.g. (b) (4) can be path dependent, defining a design space for this step only in terms of (b) (4) e.g. (b) (4) does not give a full understanding of the process. Additionally, please note that the FDA does not support use of the (b) (4) since it is not an ICH endorsed terminology. To ensure transparency and consistency moving forward indicate clearly in the submission that (b) (4)

To sum, without full evaluation of the data to support the control strategy, it is premature at this time to comment on to the adequacy of the QbD program and overall control strategy. This assessment will be a NDA review issue. See additional clarification seeking comments below and also responses to Questions 5 and 7.

Additional comments:

i. **In the NDA, clarify if the values of (b) (4) y, that are used in the (b) (4) are obtained from (b) (4) or are they (b) (4) (i.e. via equations shown on pg 132 and 139 respectively.)**
ii. **In general, confirm that the batches used for validation of models (e.g. Table 5.6.11 Dissolution) are independent i.e. not used to develop the model. Furthermore, indicate whether these batches capture possible variations expected during routine commercial manufacturing.**
iii. **Dissolution – data to support (b) (4)**
iv. **Indicate if the sampling strategy for the (b) (4) is representative of the batch size.**
v. **The sampling plan for measuring API content (b) (4) should be statistically representative. It is not clear in the meeting package how (b) (4). The use of (b) (4)**

Daiichi Sankyo Response sent on 5/16/2013:

See Appendices for Slides **6a CMA Based Design Space Approach** - (Slides 3- 22)

Meeting Discussion:

The FDA stated that monitoring (b) (4) However, the FDA has concerns with the sponsor's approach of defining a design space in terms of process

outputs i.e., (b) (4) The FDA's concern is based on the following: (a) the approach is not consistent with the ICH definition; (b) adequacy of the approach would be dependent on the frequency of measurement of (b) (4) (c) there is a risk that not all pertinent (b) (4) may be measured.

As regards site and/or equipment change, the FDA would consider a comparability protocol for equipment and/or site change and parameters. If the sponsor chooses this path, the FDA requests a discussion before submission or suggests submitting a protocol as a post approval supplement.

The sponsor asked what specifically about the (b) (4) process the FDA would like to see. FDA would like the sponsor to provide the information to support why the sponsor has chosen particular attributes and how do they affect the product. The FDA would also like the sponsor to provide details about the feedback controls.

The FDA asked if the sponsor would be willing to participate in consultative discussion with EMA or PMDA. In order for FDA to share and discuss CMC information with other Agencies, the Sponsor would have to provide consent. The purpose is to open up dialogue and discussion and work toward harmonized review approaches. The sponsor indicated that EMA is not an option (b) (4) proposed in the FDA submission. They also indicated that this product has been approved by the PMDA. The FDA asked the sponsor if we can discuss this application with our PMDA counter parts.

Daiichi Sankyo Response sent on 5/16/2013:
See Appendices for Slides - **Topic 6a (iv and v): Sampling Plan Strategy-1 (Slides 53- 61)**

See Post Meeting Feed Back (Section 3.0) for additional comments from the FDA.

6b. Current guidance, e.g. ICH Q8 Pharmaceutical Development (R2) recommend control of the (b) (4) through the (b) (4) Daiichi Sankyo has chosen to (b) (4) within design space to provide for an additional level of security taking into account the potential worst case prediction error of (b) (4) models. Does the Agency agree with the proposed (b) (4) for the edoxaban tablets?

FDA response to Question 6b:
Your approach to operate in a (b) (4) appears to be a reasonable risk based approach. Evaluation of adequacy of the proposed (b) (4) as a component of overall control strategy would be a review issue. Additionally, clarify in the NDA the following:

i. **Does the (b) (4) correspond to (b) (4) for process parameters?**
ii. **Does (b) (4), refer to the use of (b) (4)**

Daiichi Sankyo Response sent on 5/16/2013:
See Appendices for Slides - **Topic 6b(i): Relationship Between [redacted] (b) (4) (slide 23-24)**

Meeting Discussion:
The sponsor stated that [redacted] (b) (4) will be conducted in normal range.

Question7:
7a. Does the Agency agree that the proposed [redacted] (b) (4) re consistent with the FDA's current practice and appropriately defined for cGMP batch release?

FDA response to Question 7a:
The FDA assumes that the [redacted] (b) (4) (Fig. 5.7.1) is an example of how instrument failures will be dealt with also for other [redacted] (b) (4)

Although the description of [redacted] (b) (4) on page 156 mentions investigation and possible model update that follows spectral outlier detection, the proposed [redacted] (b) (4) (b) (4)

Mixing of [redacted] (b) (4) is considered acceptable once method equivalency is established, in particular for accuracy and precision attributes.

Additional relevant comments:

i. **[redacted] (b) (4) should be demonstrated to have the [redacted] (b) (4)**
ii. **The effective sample size for [redacted] (b) (4) is important and should not exceed [redacted] (b) (4)**
iii. **The number of samples used to measure [redacted] (b) (4) and the sampling plan should ensure that the true average value is measured.**
iv. **The submitted meeting package does not include description of [redacted] (b) (4) method and details such as end-point criteria. However, we would like to point out that rate of change in [redacted] (b) (4) below [redacted] (b) (4) is not considered equal to [redacted] (b) (4) better than [redacted] (b) (4) in [redacted] (b) (4). Normally for [redacted] (b) (4)**

[redacted] detected end-point, a correlation is established between changes in [redacted] characteristics such as [redacted]. However, the information submitted indicates that in [redacted] model calculation, you plan to use [redacted] regardless of true value. In such a case, demonstrate that [redacted] assures at [redacted] or less in [redacted], when measured with the appropriate sample size.

Meeting Discussion:
Due to time constraints topic was not discussed.

7b. Does the Agency agree with the strategy shown in the [redacted]

FDA response to Question 7b:
Yes, we agree. However, the [redacted] An investigation should be performed (see response to Question 7a). Also, the [redacted] is not within acceptance criteria. According to the [redacted]

Meeting Discussion:
No further discussion required.

7c. Does the Agency agree with the proposed procedure and associated [redacted]

FDA response Question 7c:
Yes, the proposed procedure and associated [redacted] appear acceptable. The implementation of [redacted] will be evaluated on-site.

Meeting Discussion:
No further discussion required.

Question 8:

8a. Does the Agency agree that setting the validation acceptance criteria as the Residual (the prediction error) and Standard Error of Prediction (the standard deviation of the Residual), consistent with the concepts in the current ASTM and EMEA guidances, are consistent with the Agency's practice and applicable to as the validation criteria for accuracy of [redacted]?

1) Residual: within [redacted]%

2) Standard error of prediction (SEP): not more than (b) (4)%

FDA response to Question 8a:

The scope of the proposed validation is acceptable; however values of proposed limits used for (b) (4) will be evaluated during the NDA review.

The FDA views are consistent with the EMA approaches described in the guidance referenced in the meeting package. The specific limits for parameters such as accuracy or precision should be justified with respect to the intended purpose of the (b) (4).

We agree with your approach described in Vol. 1, page 156 of the package, that the worst case scenario should be considered (b) (4) In view of this approach we recommend that the worst case is represented by the confidence interval derived for the multivariate calibration.

We do not consider average residuals based on calculation shown on page 169 of Vol. 1 of the package as best indicators for accuracy and precision. Normally Standard Error of Prediction is used for this purpose.

Additional relevant comments:

i. **The FDA considers the number of latent variables in the multivariate model an important parameter that helps avoiding over-fitting. Detailed justification of this parameter should be included in the application.**
ii. **It is noticed that the formulae for standard error of prediction (SEP) and residuals (page 168) are not correct. Calculations should be done on (b) (4) (b) (4)**
iii. **(b) (4) is considered a (b) (4). Since your design space allows a wide range of (b) (4), the robustness of (b) (4) over the entire range of (b) (4) should be established during validation.**

Daiichi Sankyo Response sent on 5/16/2013:

See Appendices for Slides - Topic 8a(ii): Calculation Procedure of SEP (Slides 26-28)

Meeting Discussion:

The FDA stated that data averaging method used for calibration samples, validation samples, and in routine prediction should be the same. Since the information submitted in the package was limited, this consistency was not apparent.

8b. Does the Agency also agree that the validation criterion for accuracy of the dissolution model may be set as the Residual (prediction error) consistent with the justification provided?

FDA response to Question 8b:

i. **There is insufficient information in the meeting package to reach a conclusion on the adequacy of your proposal. To support the use of** (b) (4)

ii. **Note that FDA considers UV-Vis to be a less specific detection method for the quantitation of your drug substance and recommends that you either develop a suitable HPLC method to support dissolution testing or provide rationale for the use of UV-Vis for your drug product.**

iii. **The acceptability of the validation criterion range will be a review issue.**

Meeting Discussion:
Due to time constraints topic was not discussed. See post meeting comments.

Question 9:
Does the Agency agree with the proposed post-approval change management for the (b) (4)

FDA response to Question 9:
Insufficient information is provided in the submission for the FDA to evaluate the potential risks of all proposed post approval changes and to determine the adequacy of the proposed regulatory filing category. Please note that in accordance with 21 CFR 314.70 (e) you can consider submitting the proposed post approval change management strategy in the submission as a 'Change Protocol', where the protocol includes information to demonstrate the lack of adverse effect of the proposed change(s) on the identity, strength, quality, purity, and potency of the drug product. However, given some precedence setting aspects of your application, it is recommended that you discuss your protocol approach with the FDA prior to submission. Additionally, change protocols may be submitted either in the NDA or as a Prior Approval Supplement.

Meeting Discussion:
No further discussion required.

Question 10:
Does the Agency agree to the proposal to (b) (4) stability specifications and annual stability protocols, based on a comparability protocol to be submitted in the original NDA, (b) (4)

(b) (4)

FDA response Question 10:
No. You can submit the comparability protocol in the original NDA for the proposal to (b) (4) **. However, due to the limited experience in commercial manufacturing and lack of sufficient stability data for the commercial drug product, we don't agree with your proposal** (b) (4)

Meeting Discussion:
No further discussion required.

Question 11:
Daiichi Sankyo would like to submit (b) (4) edoxaban tablets (15 mg, 30 mg and 60 mg) in the NDA. Is this acceptable to the Agency?

FDA response to Question 11:
No. Per 21 CFR 314.50(d)(1)(ii)(b), submit executed batch records for each batch of drug product used to conduct a primary stability study, written in the English language. Also, in accordance with CFR 314.50 either submit a Master Batch Record (MBR) or a comparably detailed manufacturing process description.

Meeting Discussion:
No further discussion required.

Question 12:
12a. In the event Daiichi Sankyo files a single NDA for edoxaban tablets for two indications, Atrial Fibrillation and Venous Thromboembolism, for which the clinical and non-clinical sections would be reviewed by both Hematology and Cardiovascular and Renal Divisions, the Sponsor requests clarification on how the CMC review will be conducted? For example, will the drug product CMC section be subject to a single review by the CMC QbD expert group and the drug substance CMC section be subject to a single review within either division?

FDA Response to Question 12a:
A determination of how the application will be handled administratively and how the CMC review will be conducted will be established at the time of submission. The CMC review for two different indications will be harmonized.

Meeting Discussion:
No further discussion required.

12b. As per 314.50 (d)(1)(iv), Daiichi Sankyo would like to propose a "rolling submission" approximately 3 months prior to the NDA submission to allow for ample time for the QbD review. Will the Agency support a "rolling submission" of Module 3 with the understanding that under 314.50 (d)(1)(iv) that the review will commence dependent upon available resources? Can the Division project the likelihood that the CMC review will commence at the time of CMC submission under the current working paradigms of "the program" under PDUFA V?

FDA Response to Question 12b:

Yes, the NDA may be submitted as a rolling submission. The rolling submission would give the CMC reviewers an opportunity to get a head start on review of the submission. However, actual timing of commencement of the CMC review will depend on available resources.

Additional Comments:

i. **The clinical manufacturing site for drug product is identified as (b) (4) in the meeting package. It is also identified as the site at which the nine primary stability/registration batches of product were manufactured at pilot scale ((b) (4) the proposed commercial scale). However, the commercial manufacturing site is not identified. While various tables in the meeting package refer to Site A and Site B for drug product manufacturing – for example Table 5.6.18 "*Manufacturing Equipment of Different Manufacturing Scales and Sites*", lists Site A and Site B for manufacture of commercial scale (b) (4) kg) tablets, utilizing different equipment and Table 5.6.1 (b) (4) " lists the same sites utilizing different ranges – no identification of Site A and Site B is provided.**

   If the site for commercial manufacturing is different from the site at which registration batches were manufactured, provide supporting data in the submission to address plans to mitigate following potential risks:

   a. **Applicability of the (b) (4) and dissolution model at the commercial site, including measurement considerations for relevant (b) (4) . (b) (4) for dissolution and (b) (4) can be used if the site-specific validation demonstrates that the model predictions are reliable irrespective of site, otherwise specific models should be developed.**
   b. **Since it is proposed (b) (4) , provide available data (b) (4)**

ii. **Two blister pack packaging configurations are proposed – 7ct and 10ct. Provide stability data for each configuration or justify their exclusion.**

Meeting Discussion:
No further discussion required.

The following additional comments are regarding dissolution:

iii. **It is noted that the dissolution model does not take into consideration the impact of [redacted] Revise your dissolution model accordingly.**

iv. **Evaluate the predictive power of the proposed dissolution model using batches that failed dissolution acceptance criterion. The need for this data is evident since throughout the laboratory and [redacted] to determine the design space, the dissolution profiles from the batches tested are similar. In addition, the [redacted] for the predictive dissolution model showed a relatively narrow range of the observed value (i.e. [redacted] % dissolution) with the majority of observations being within the range of [redacted] %.**

v. **Evaluate the predictive power of the model using batches that failed in vivo BE, if available.**

vi. **In the absence of information described in bullets iii and iv calibrate the dissolution model using batches that do not meet the dissolution acceptance criterion.**

vii. **We highly recommend a cross-validation approach to further verify the robustness of the model.**

viii. **Submit the following data for verification of the dissolution model:**
   a. **Step by step model development procedure**
   b. **Raw data including both model inputs and outputs used for model development and validation**

ix. **There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed design space, manufacturing scales and sites would result in products that are bioequivalent. Submit adequate justification, including (but not limited to) the following information:**
   a. **f2 statistical testing for edoxoban tablets 15 mg, 30 mg and 60 mg dissolution profile comparisons of tablets manufactured across the proposed design space for the [redacted]**
   b. **f2 statistical testing for edoxoban tablets dissolution profile comparisons of tablets manufactured at different manufacturing sites (provide the comparisons using the clinical batches as reference). We remind you that major changes in process parameters and drug product composition should be supported with BE data.**

Meeting Discussion:
No further discussion required.

3.0 POST MEETING FEEDBACK

During the meeting, the FDA agreed to provide post meeting feedback on the following items: Starting material (b) (4) (Q1), Dissolution (Q8b1), Sampling plan (Q6a iv and v). Feedback on each item is provided below.

Starting material (b) (4) (Q1):
Based on review of the additional justification for the acceptability of (b) (4) as a starting material submitted on 03-June-2013 by email to Jewell Martin, Regulatory Project Manager, and subsequent internal discussion, we reiterate our preliminary comment dated 13-May-2013 provided in response to the Pre-NDA meeting package and our advice at the face-to-face Pre-NDA meeting 17-May-2013 that:

(b) (4) it is recommended that it be designated (b) (4) as proposed. (b) (4)

Also, to clarify, the FDA did not agree to your previous proposal to designate (b) (4) as a starting material at the EOP2 meeting in 2008, as per the official meeting minutes which state that "…a final determination will be made during the NDA review."

Please note that, if the same proposal is submitted in the NDA, it may be a significant review issue.

Dissolution (Q8b1):
During the meeting the FDA recommended to provide BA/BE data to support the proposed acceptance criterion of Q= (b) (4) % at 30 min. At the conclusion of the meeting, the sponsor approached the Biopharmaceutics reviewer and inquired about the specifics on the in vivo data needed to further support the proposed dissolution acceptance criterion of Q= (b) (4) % at 30 min. The Sponsor asked whether a (b) (4) would be adequate. The FDA responded that this approach would not be adequate for the purpose of setting dissolution specifications and added that a BE study comparing a formulation of the same product with slower release characteristics than those for the to-be-marketed (proposed) formulation would be typically be used. The Sponsor mentioned that they have such information and that they would be submitting it in support of their proposal.

With respect to topic 8b (1), the sponsor provided the following response on slide 63 which was not discussed during the face-to-face meeting:

[redacted] (b) (4)

After further consideration, the FDA considers that the use of only residuals for validation purposes is acceptable.

Sampling Plan (Q6a iv and v):
The sampling approach for the [redacted] (b) (4) including frequency and sample size should be such that it represents the quality of an entire commercial scale batch.

5.0 ACTION ITEMS

The FDA will be seeking consent from the sponsor to discuss this application with our PMDA counter parts.

6.0 ATTACHMENTS AND HANDOUTS

Handouts provided by Daiichi Sankyo on May 16, 2013, see attached.

7.0 CONCURRENCE

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

JEWELL D MARTIN
06/14/2013

ALI H AL HAKIM
06/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 63266 and IND 77254

MEETING PRELIMINARY COMMENTS

Daiichi Sankyo, Inc.
Attention: Linda Nelson, PhD
Director, Regulatory Affairs, CMC
399 Thornall Street
Edison, NJ 08837

Dear Dr. Nelson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Edoxaban (DU-176b) Tablets.

We also refer to your February 1, 2013, correspondence, received February 4, 2013, requesting a Type B Pre-NDA meeting to discuss specific CMC topics and provide overviews of the strategies that will be incorporated to support the registration of the Edoxaban NDA and to ensure that Diiachi Sanyko incorporates FDA comments from both branches in their development plans.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment
Food and Drug Administration

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA, CMC
Meeting Date and Time:	May 17, 2013, 9:00AM-10:30AM (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 63266 and IND 77254
Product Name:	Edoxaban (DU-176b) Tablets
Indication:	Treatment of (b) (4) venous thromboembolism (VTE) and (b) (4) pulmonary embolism
Sponsor/Applicant Name:	Daiichi Sankyo, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 17, 2013, 9:00AM-10:30AM (EST), FDA White Oak Campus between Daiichi Sankyo, Inc. and the Division of New Drug Quality Assessment I. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

On February 4, 2013, the Agency received correspondence from Daiichi Sankyo, Inc. requesting a Type B meeting to discuss specific CMC topics and provide overviews of the strategies that will be incorporated to support the registration of the Edoxaban NDA and to ensure that Diiachi Sanyko incorporates FDA comments from both branches in their development plans. The

Agency accepted the request and issued a Meeting Granted letter on February 14, 2013. The meeting package was received March 20, 2013.

The face to face meeting with Daiichi Sankyo, Inc. was initially scheduled to occur on April 17, 2013. After reviewing the meeting package, the Agency determined that additional expertise was necessary. After discussion with the sponsor, the meeting date was changed to May 17, 2013, in order to accommodate scheduling for Daiichi Sankyo, Inc. meeting participants and Agency meeting participants.

2.0 DISCUSSION

Question 1

Does the revision of the specifications for (b) (4) starting material satisfy the recommendations made by the Agency at the EOP 2 meeting? Specifically, is Daiichi Sankyo's approach to setting the acceptance criteria for related substances and residual solvents based on spike and recovery experiments acceptable to the Agency?

FDA response to Question 1:

(b) (4) **it is recommended that it be designated** (b) (4) **as proposed.** (b) (4)

Question 2

2a. Does the Agency agree with the completeness and acceptability of tests proposed for edoxaban tosylate drug substance release?

FDA response to Question 2a:

Insufficient information is provided at this time to determine acceptability of the proposed (b) (4) **This will be a review issue. Find below some additional comments for your consideration:**

- **i. Include an** (b) (4)
- **ii. Expand the** (b) (4) **or justify their exclusion with data.**
- **iii. Include a test for the** (b) (4) **or justify its' exclusion with data.**

2b. Does the Agency agree with the proposed control strategy for (b) (4) impurities where testing for these compounds will not be performed on edoxaban tosylate drug substance? Further, is the proposed data set outlined above sufficient to support the proposed control strategy?

FDA response to Question 2b:
The proposed control strategy for [redacted] impurities appears to be acceptable, but the final assessment will be a review issue. Of particular concern are the in-process controls for [redacted].

2c. Does the Agency agree with the proposed control strategy for known genotoxic impurities (GTIs) that are controlled in the individual starting materials, specifically [redacted], and not in the final drug substance? Further, is the proposed data set outlined below sufficient to support the proposed control strategy?

FDA response to Question 2c:
No. The proposed control strategy does not includ [redacted] For the risk associated with genotoxic impurities particularly [redacted] would be expected unless otherwise justified.

For the evaluation of the potential genotoxic impurities using a [redacted], it is recommended that two different SAR prediction methods be applied, such as an expert rule-based and a statistical-based model. It appears that you only used DEREK, i.e. an expert rule-based approach. A statistical-based model should be used in addition to DEREK. Please submit the SAR analyses for our review in the NDA; include the version of DEREK used. Your decision to strictly control [redacted] as a potential genotoxic impurity based on the positive result in DEREK is acceptable.

The proposed acceptance criteria for the genotoxic impurities [redacted] in [redacted] of NMT [redacted]% are expected to result in levels < [redacted]ppm (the limit of quantitation) in the edoxaban drug substance. Based on the information rovided and the summary tables of your spike/recovery studies, the acceptance criteria for genotoxic impurities [redacted] ppm for the maximum dose of 60 mg/day are acceptable.

2d. Does the Agency agree with the control strategy for genotoxic impurities arising during [redacted] edoxaban tosylate? Further, is the proposed data set outlined sufficient to support the proposed control strategy? Finally, does the Agency agree that a comparability protocol and CBE-30 supplement may be submitted [redacted]

FDA response to Question 2d:

i. **Regarding control strategy – this may acceptable provided sufficient supportive data is provided. The final assessment will be a review issue.**
ii. **Regarding the data set – release batch data for [redacted] may be indicated to support its' exclusion from release specifications.**
iii. **No, we do not agree with your proposal of submitting a comparability protocol and CBE-30 supplement [redacted] We recommend that you submit a prior approval supplement with data to support [redacted]**

iv. **Regarding the genotoxic impurities [redacted] that arise from [redacted], the proposed acceptance criteria of NMT [redacted] ppm for the total of all three impurities is acceptable based on the [redacted] ppm for the maximum dose of 60 mg/day.**

Question 3

Does the Agency agree that the data package for the primary registration stability manufactured at [redacted] is adequate to establish a retest period for the drug substance manufactured at the [redacted] commercial site, if equivalence is shown with 9 months site-specific stability data for three lots from full-scale commercial manufacturing at [redacted]?

FDA response to Question 3:

Yes. The retest period will be a NDA review issue.

Question 4

Does the Agency agree that the current stability program, consistent with ICH Q1A, Q1B and Q1D, and that the validation protocol and post-approval annual batch protocols are acceptable?

FDA response to Question 4:

i. **Regarding current stability program for drug product – the meeting package indicated that the proposed primary stability batches (tablets) were manufactured at pilot scale [redacted] of the commercial) with two lots of clinical drug substance [redacted] packaged in the to-be-marketed configuration. Eighteen to twenty four months of long-term stability data will be submitted in the NDA. This proposal may be acceptable provided the primary stability batches were manufactured using the commercial process.**

ii. **Regarding the stability protocol: [redacted] proposals are included in the meeting package (Option 1 Table 5.4.7 and Option 2 Table 5.4.8) - Option 1 does not include [redacted] Option 2 includes the 7 ct bottle presentation and omits 30mg (mid-strength) tablets in all packaging presentations plus the 30 ct bottle at all three strengths. This design appears to be consistent with Q1D and may be acceptable provided the stability data of the extremes in the bracketing design are comparable, which will be a review issue.**

iii. **Regarding the post-approval protocol: The annual batch stability protocol should also include 3, 6, 9, and 18 months time points. The [redacted] proposal [redacted] Please note this design is unacceptable. A similar design as Option 2 (Table 5.4.8 in the submission) is scientifically more reasonable and the 7 count bottle should be included.**

Question 5

5a. Does the Agency agree with the completeness of the list of tests proposed for edoxaban drug product release and stability? Specifically, the (b) (4) will not be performed (b) (4) per the agreement reached with the Agency at the Type "C" meeting to allow for (b) (4)

FDA response Question 5a:

Your proposal to include a rationale in the NDA to support your proposal (b) (4) appears to be reasonable. However, insufficient information is provided at this time to assess the acceptability of (b) (4), as proposed. This will be a review issue.

Additional comments:

i. **Justify the proposal to (b) (4) on release and stability by data.**
ii. **Your proposal to notify updates about (b) (4) (refer footnote (a) of table 5.5.2) is not adequate. These models are regarded as high impact models, (b) (4) are sole indicators of bioavailability of the finished product. Hence, changes to these models have a potential to adversely affect product quality and should be notified to the Agency in accordance with 21 CFR 314.70.**

5b. Does the Agency agree with the format of the proposed specifications for (b) (4)

FDA response to Question 5b:

It is suggested to combine Tables 5.5.1 (b) (4) into a single table indicating which analytical tests would be applicable for (b) (4). Also indicate the methods that will be used for routine commercial production and those that are alternate. Additionally, since values for (b) (4) include values of these (b) (4) on the specification sheet, indicating that these are (b) (4) Note that Table 5.5.2 (b) (4) which should be included regardless of which (b) (4)

We noticed that the calculation you propose for uniformity of dosage units is based on (b) (4) and uses (b) (4) acceptance limit. However, while the (b) (4) method is based on measuring the active content of individual tablets, your proposed procedure relies on an (b) (4) As indicated during the 2010 face to face meeting, the Agency perceives that there is a risk due to (b) (4), and we recommend that in addition to the data provided in the meeting package (e.g. table 5.6.7 and Fig 5.6.19), you provide data from commercial scale batches showing a one on one comparison of active content of individual tablets measured by the traditional method (e.g. HPLC) versus your method , for a statistically significant number of tablets from each batch.

Furthermore, our simulation indicates that your proposed procedure yields results of acceptance values for [redacted] on the same input values. You should re-evaluate and justify the acceptance limit.

5c. Does the Agency agree with the approach to setting the dissolution acceptance criteria for [redacted] as Q= [redacted]% and [redacted] as not less than [redacted]%?

FDA response to Question 5c:

i. Your approach for setting the dissolution acceptance criterion for [redacted] is not acceptable. Note that since the acceptance criterion for [redacted] is based on the acceptability of the criterion for conventional testing, it is also not acceptable.

ii. The acceptance criterion [redacted] should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12). Data from the bio-batches (pivotal phase 3 & PK) and registration stability batches should be used for the setting of the dissolution acceptance criterion.

iii. Also, there is not sufficient information to make a recommendation on an adequate dissolution acceptance criterion. A preliminary evaluation indicates that a criterion of Q= [redacted]% at [redacted]min might be more appropriate for your product and will improve the di rimin ng capability of the method. Provide the following information:

- **a. Complete dissolution profile data (raw data and mean values) from the pivotal Phase 3 clinical and registration batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.**
- **b. Individual and mean values in tabulated form and graphical form (mean values) for all the batches listed in Table 5.5.6.**
- **c. Data demonstrating that the proposed dissolution acceptance criterion is able to reject batches outside the ranges of your proposed design space (e.g. drug products that are intentionally manufactured with meaningful variations, i.e., ± [redacted]% change to the specification-ranges) for the most critical manufacturing variables (e.g. [redacted]**
- **d. If available, submit data showing the capability of the selected dissolution method/acceptance criterion to reject batches that are not bioequivalent.**
- **e. Provide data demonstrating the discriminating ability of the dissolution method to detect the presence of the most relevant [redacted] in the drug product. Include a complete assessment of the apparent pH dependent solubility, inherent dissolution rate, the ability of the proposed dissolution method to screen for [redacted] in the drug product and a discussion (with supporting data) on the clinical impact of [redacted]**
- **f. The criterion for the [redacted] should be based on passing the acceptance criterion based not only on mean values but also**

when both the minimum and maximum values for each variable are incorporated in the model.

Question 6

Based on Daiichi Sankyo's understanding of the recommendations, listed above, provided by the Agency at the Type "C" meeting, Daiichi Sankyo seeks concurrence with the approaches taken to address the Agency's recommendations.

6a. Does the Agency agree that the refinements made to the QbD program address the previous Agency comments and that the proposed [redacted] (b) (4) ?

FDA response Question 6a:

The information submitted does appear to respond to some previous Agency comments regarding the QbD program (e.g. [redacted] (b) (4)). Regarding the proposed [redacted] (b) (4) based design space, the Agency views your strategy of monitoring [redacted] (b) (4) The Agency would like to remind you to define design space in concurrence with ICH Q8 (R2) in terms of input parameters not output parameters e.g. [redacted] (b) (4) . Since some processes e.g. [redacted] (b) (4) can be path dependent, defining a design space for this step only in terms of [redacted] (b) (4) e.g. [redacted] (b) (4) does not give a full understanding of the process. Additionally, please note that the Agency does not support use of the [redacted] (b) (4) since it is not an ICH endorsed terminology. To ensure transparency and consistency moving forward indicate clearly in the submission that [redacted] (b) (4)

To sum, without full evaluation of the data to support the control strategy, it is premature at this time to comment on to the adequacy of the QbD program and overall control strategy. This assessment will be a NDA review issue. See additional clarification seeking comments below and also responses to Questions 5 and 7.

Additional comments:

i. **In the NDA, clarify if the values of [redacted] (b) (4) that are used in the [redacted] (b) (4) , are obtained from [redacted] (b) (4) or are they [redacted] (b) (4) (i.e. via equations shown on pg 132 and 139 respectively.)**
ii. **In general, confirm that the batches used for validation of models (e.g. Table 5.6.11 Dissolution) are independent i.e. not used to develop the model. Furthermore, indicate whether these batches capture possible variations expected during routine commercial manufacturing.**
iii. **Dissolution – data to support [redacted] (b) (4)**
iv. **Indicate if the sampling strategy for the [redacted] (b) (4) is representative of the batch size.**

v. **The sampling plan for measuring API content [redacted] should be statistically representative. It is not clear in the meeting package how [redacted]**

6b. Current guidance, e.g. ICH Q8 Pharmaceutical Development (R2) recommend control of the [redacted] through the [redacted]. Daiichi Sankyo has chosen to [redacted] within design space to provide for an additional level of security taking into account the potential worst case prediction error of [redacted] models. Does the Agency agree with the proposed [redacted] for the edoxaban tablets?

FDA response to Question 6b:
Your approach to operate in a [redacted] appears to be a reasonable risk based approach. Evaluation of adequacy of the proposed [redacted] as a component of overall control strategy would be a review issue. Additionally, clarify in the NDA the following:

i. **Does the [redacted] correspond to [redacted] for process parameters?**
ii. **Does [redacted], refer to the use of [redacted]?**

Question 7

7a. Does the Agency agree that the proposed [redacted] are consistent with the FDA's current practice and appropriately defined for cGMP batch release?

FDA response to Question 7a:
The Agency assumes that the [redacted] (Fig. 5.7.1) is an example of how instrument failures will be dealt with also for other [redacted].

Although the description of [redacted] on page 156 mentions investigation and possible model update that follows spectral outlier detection, the proposed [redacted]

Mixing of [redacted] is considered acceptable once method equivalency is established, in particular for accuracy and precision attributes.

Additional relevant comments:

i. **[redacted] should be demonstrated to have the [redacted]**

ii. **The effective sample size for [redacted] is important and should not exceed [redacted]**

iii. **The number of samples used to measure [redacted] and the sampling plan should ensure that the true average value is measured.**

iv. **The submitted meeting package does not include description of [redacted] method and details such as end-point criteria. However, we would like to point out that rate of change in [redacted] below [redacted] is not considered equal to [redacted] better than [redacted] in [redacted]. Normally for [redacted] detected end-point, a correlation is established between changes in [redacted] characteristics such as [redacted] However, the information submitted indicates that in [redacted] model calculation, you plan to use [redacted], regardless of true value. In such a case, demonstrate that [redacted] assures at [redacted] or less in [redacted] when measured with the appropriate sample size.**

7b. Does the Agency agree with the strategy shown in the [redacted]?

FDA response to Question 7b:
Yes, we agree. However, the [redacted]. An investigation should be performed (see response to Question 7a). Also, the [redacted] is not within acceptance criteria. According to the [redacted]

7c. Does the Agency agree with the proposed procedure and associated [redacted]?

FDA response Question 7c:
Yes, the proposed procedure and associated [redacted] appear acceptable. The implementation of [redacted], will be evaluated on-site.

Question 8

8a. Does the Agency agree that setting the validation acceptance criteria as the Residual (the prediction error) and Standard Error of Prediction (the standard deviation of the Residual), consistent with the concepts in the current ASTM and EMEA guidances, are consistent with the Agency's practice and applicable to as the validation criteria for accuracy of [redacted]

1) Residual: within ± [redacted]
2) Standard error of prediction (SEP): not more than [redacted]

FDA response to Question 8a:

The scope of the proposed validation is acceptable; however values of proposed limits used for [redacted] will be evaluated during the NDA review.

The Agency views are consistent with the EMA approaches described in the guidance referenced in the meeting package. The specific limits for parameters such as accuracy or precision should be justified with respect to the intended purpose of the [redacted].

We agree with your approach described in Vol. 1, page 156 of the package, that the worst case scenario should be considered [redacted] In view of this approach we recommend that the worst case is represented by the confidence interval derived for the multivariate calibration.

We do not consider average residuals based on calculation shown on page 169 of Vol. 1 of the package as best indicators for accuracy and precision. Normally Standard Error of Prediction is used for this purpose.

Additional relevant comments:

i. **The Agency considers the number of latent variables in the multivariate model an important parameter that helps avoiding over-fitting. Detailed justification of this parameter should be included in the application.**
ii. **It is noticed that the formulae for standard error of prediction (SEP) and residuals (page 168) are not correct. Calculations should be done on [redacted].**
iii. **[redacted] is considered a [redacted] Since your design space allows a wide range of [redacted], the robustness of [redacted] over the entire range of [redacted] should be established during validation.**

8b. Does the Agency also agree that the validation criterion for accuracy of the dissolution model may be set as the Residual (prediction error) consistent with the justification provided?

FDA response to Question 8b:

i. **There is insufficient information in the meeting package to reach a conclusion on the adequacy of your proposal. To support the use of [redacted]**

(b) (4)

ii. **Note that FDA considers UV-Vis to be a less specific detection method for the quantitation of your drug substance and recommends that you either develop a suitable HPLC method to support dissolution testing or provide rationale for the use of UV-Vis for your drug product.**

iii. **The acceptability of the validation criterion range will be a review issue.**

Question 9

Does the Agency agree with the proposed post-approval change management for the (b) (4)

FDA response to Question 9:

Insufficient information is provided in the submission for the Agency to evaluate the potential risks of all proposed post approval changes and to determine the adequacy of the proposed regulatory filing category. Please note that in accordance with 21 CFR 314.70 (e) you can consider submitting the proposed post approval change management strategy in the submission as a 'Change Protocol', where the protocol includes information to demonstrate the lack of adverse effect of the proposed change(s) on the identity, strength, quality, purity, and potency of the drug product. However, given some precedence setting aspects of your application, it is recommended that you discuss your protocol approach with the Agency prior to submission. Additionally, change protocols may be submitted either in the NDA or as a Prior Approval Supplement.

Question 10

Does the Agency agree to the proposal to (b) (4)

to be submitted in the original NDA, (b) (4)

FDA response Question 10:

No. You can submit the comparability protocol in the original NDA for the proposal to (b) (4) However, due to the limited experience in commercial manufacturing and lack of sufficient stability data for the commercial drug product, we don't agree with your proposal (b) (4)

Question 11
Daiichi Sankyo would like to submit (b) (4) edoxaban tablets (15 mg, 30 mg and 60 mg) in the NDA. Is this acceptable to the Agency?

FDA response to Question 11:
No. Per 21 CFR 314.50(d)(1)(ii)(b), submit executed batch records for each batch of drug product used to conduct a primary stability study, written in the English language. Also, in accordance with CFR 314.50 either submit a Master Batch Record (MBR) or a comparably detailed manufacturing process description.

Question 12
12a. In the event Daiichi Sankyo files a single NDA for edoxaban tablets for two indications, Atrial Fibrillation and Venous Thromboembolism, for which the clinical and non-clinical sections would be reviewed by both Hematology and Cardiovascular and Renal Divisions, the Sponsor requests clarification on how the CMC review will be conducted? For example, will the drug product CMC section be subject to a single review by the CMC QbD expert group and the drug substance CMC section be subject to a single review within either division?

FDA Response to Question 12a:
A determination of how the application will be handled administratively and how the CMC review will be conducted will be established at the time of submission. The CMC review for two different indications will be harmonized.

12b. As per 314.50 (d)(1)(iv), Daiichi Sankyo would like to propose a "rolling submission" approximately 3 months prior to the NDA submission to allow for ample time for the QbD review. Will the Agency support a "rolling submission" of Module 3 with the understanding that under 314.50 (d)(1)(iv) that the review will commence dependent upon available resources? Can the Division project the likelihood that the CMC review will commence at the time of CMC submission under the current working paradigms of "the program" under PDUFA V?

FDA Response to Question 12b:
Yes, the NDA may be submitted as a rolling submission. The rolling submission would give the CMC reviewers an opportunity to get a head start on review of the submission. However, actual timing of commencement of the CMC review will depend on available resources.

Additional Comments:

i. **The clinical manufacturing site for drug product is identified as (b) (4) in the meeting package. It is also identified as the site at which the nine primary stability/registration batches of product were manufactured at pilot scale ((b) (4) the proposed commercial scale). However, the commercial manufacturing site is not identified. While various tables in the meeting package refer to Site A and Site B for drug product manufacturing – for example Table 5.6.18 "*Manufacturing Equipment of Different Manufacturing Scales and Sites*", lists Site A and Site B for manufacture**

of commercial scale [redacted] kg) tablets, utilizing different equipment and Table 5.6.1 "[redacted] lists the same sites utilizing different ranges – no identification of Site A and Site B is provided.

If the site for commercial manufacturing is different from the site at which registration batches were manufactured, provide supporting data in the submission to address plans to mitigate following potential risks:

- **a. Applicability of the [redacted] and dissolution model at the commercial site, including measurement considerations for relevant [redacted] for dissolution and [redacted] can be used if the site-specific validation demonstrates that the model predictions are reliable irrespective of site, otherwise specific models should be developed.**
- **b. Since it is proposed [redacted], provide available data [redacted]**

ii. Two blister pack packaging configurations are proposed – 7ct and 10ct. Provide stability data for each configuration or justify their exclusion.

The following additional comments are regarding dissolution:

iii. It is noted that the dissolution model does not take into consideration the impact of [redacted]. Revise your dissolution model accordingly.

iv. Evaluate the predictive power of the proposed dissolution model using batches that failed dissolution acceptance criterion. The need for this data is evident since throughout the laboratory and [redacted] to determine the design space, the dissolution profiles from the batches tested are similar. In addition, the [redacted] for the predictive dissolution model showed a relatively narrow range of the observed value (i.e. [redacted] % dissolution) with the majority of observations being within the range of [redacted] %.

v. Evaluate the predictive power of the model using batches that failed in vivo BE, if available.

vi. In the absence of information described in bullets iii and iv calibrate the dissolution model using batches that do not meet the dissolution acceptance criterion.

vii. We highly recommend a cross-validation approach to further verify the robustness of the model.

viii. Submit the following data for verification of the dissolution model:

- **a. Step by step model development procedure**
- **b. Raw data including both model inputs and outputs used for model development and validation**

ix. There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed design space, manufacturing scales and sites would result in products that are

bioequivalent. Submit adequate justification, including (but not limited to) the following information:

a. **f2 statistical testing for edoxoban tablets 15 mg, 30 mg and 60 mg dissolution profile comparisons of tablets manufactured across the proposed design space for the** (b) (4)
b. **f2 statistical testing for edoxoban tablets dissolution profile comparisons of tablets manufactured at different manufacturing sites (provide the comparisons using the clinical batches as reference). We remind you that major changes in process parameters and drug product composition should be supported with BE data.**

3.0 CONCURRENCE

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

JEWELL D MARTIN
05/13/2013

ALI H AL HAKIM
05/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77254

MEETING MINUTES

Daiichi-Sankyo Inc.
Attention: David Kao, RPh, MBA
Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Mr. Kao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for edoxaban (DU-176b).

We also refer to the teleconference between representatives of your firm and the FDA on 10 December 2012. The purpose of the meeting was to discuss your planned pharmacogenomics analyses to be conducted upon the conclusion of your ongoing trial, 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 - **E**ffective a**N**ticoa**G**ulation with factor x**A** next **G**Eneration in **A**trial **F**ibrillation (**ENGAGE AF-TIMI** 48)".

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alison Blaus, Regulatory Project Manager at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Rajnikanth Madabushi, Ph.D.
Team Leader
Division of Clinical Pharmacology I
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor's Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance
Meeting Date and Time:	10 December 2012 from 1300 – 1400 EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 77254
Product Name:	edoxaban (DU-176b)
Indication:	Nonvalvular atrial fibrillation
Sponsor Name:	Daiichi-Sankyo
Meeting Chair:	Rajnikanth Madabushi, Ph.D.
Meeting Recorder:	Alison Blaus

FDA ATTENDEES

* *CDER, Office of New Drugs, Division of Cardiovascular & Renal Products*

Stephen Grant, MD	Deputy Director
Preston Dunnmon, MD	Clinical Reviewer
Alison Blaus, RAC	Regulatory Health Project Manager

* *CDER, Office of Clinical Pharmacology*

Rajnikanth Madabushi, PhD	Team Leader, Division of Clinical Pharmacology I
Mike Pacanowski, PharmD, MPH	Genomics Team Leader
Hobart Rogers, PharmD, PhD	Genomics Reviewer

* *CDER, Office of Biostatistics*

Sue Jane Wang, PhD	Associate Director
James Hung, PhD	Director, Division of Biometrics I
John Lawrence, PhD	Mathematical Statistician

* *CDRH, Office of In Vitro Diagnostics and Radiological Health*

Elizabeth Mansfield, PhD	Director, Personalized Medicine

DAIICHI-SANKYO ATTENDEES

Joseph Walker, PharmD	Sr. Director, Companion Dx & Pharmacogenomics Translational Medicine & Clinical Pharmacology
Alexander Vandell, PharmD, PhD	Senior Scientist, Clinical Pharmacogenomics Translational Medicine & Clinical Pharmacology
Dolly Parasrampuria, PhD	Senior Director, Clinical Pharmacology
Karen S. Brown, PhD	Executive Director, Clinical Pharmacology
Hans J. Lanz, MD	Executive Director, Cardiovascular Clinical Development
Youngsook Choi, MD	Senior Director, Clinical Safety & Pharmacovigilance
Minggao Shi, PhD	Senior Director, Biostatistics
Doreen Morgan, PharmD, MS	Executive Director, Regulatory Affairs
David Kao, RPh, MBA	Director, Regulatory Affairs

1.0 BACKGROUND

Edoxaban (DU-176b) is an orally administered inhibitor of coagulation Factor Xa, being developed to reduce the risk of stroke and systemic embolic events (SEEs) in patients with non-valvular atrial fibrillation (AF). The sponsor is conducting, in conjunction for TIMI study group, one pivotal Phase 3 trial (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 - **E**ffective a**N**ticoa**G**ulation with factor x**A** next **G**Eneration in **A**trial **F**ibrillation (**ENGAGE AF-TIMI 48**)". TIMI 48 is an event driven trial, but is anticipated to be completed in 1Q 2013.

The sponsor's goal for this meeting was to gain Agency insight on the results from their Phase 2 program (PRT018), their proposed pharmacogenomics analysis plan for ENGAGE AF-TIMI 48, and to gain an understanding of the potential impact of these data on labeling. The sponsor presented a few slides at the 10 December 2012 meeting. These slides can be found as an appendix to these minutes.

2. DISCUSSION

Preamble

Your proposed pharmacogenomic substudy of ENGAGE-48 may add to what is already known about the genotypic variation in response to warfarin and we are willing to review the protocol. However, we believe that it is unlikely (b) (4), should it be approved for marketing in the USA. The study will be fundamentally a study of warfarin using edoxaban as a comparator. The genotypic variation in response to warfarin is already described in the warfarin label. (b) (4)

2.1. Questions for the Agency

1. We plan to use the *VKORC1* -1639 G>A (rs9923231) and *CYP2C9* *2 (rs1799853) and *3 (rs1057910) alleles to define individuals that are more sensitive to warfarin and at increased risk for bleeds. Does the Agency agree that these SNPs are sufficient?

   FDA Preliminary Response

   Yes.

   Discussion at the Meeting

   No further discussion at the meeting.

2. The purpose of our PGx analysis will be to generate data which are informational to clinicians and could potentially be included in the product labeling. We do not intend to develop a companion diagnostic. Therefore, we propose to genotype samples using analytically validated TaqMan-based assays at a CLIA-certified commercial laboratory. Does the Agency agree that the platform and lab are sufficient for the proposed intent of the analyses?

FDA Preliminary Response
Yes. Please submit a summary of the analytical validation for your assays.

Discussion at the Meeting
No further discussion at the meeting.

3. For the statistical analysis, we propose to divide subjects into two groups, normal warfarin responders (~63% of the population) and warfarin sensitive (~37% of the population), using their *VKORC1* and *CYP2C9* genotypes and the table in the U.S. warfarin package insert. Does the Agency agree with our binning approach?

FDA Preliminary Response
Consider an analysis dividing subjects into the 3 groups similar to the dose groups described in the warfarin package insert.

Discussion at the Meeting
No further discussion at the meeting.

4. Does the Agency have any comments on the planned pharmacogenomic analysis of ENGAGE AF-TIMI48?

FDA Preliminary Response
We encourage you to follow your pre-specified statistical analysis plan for both efficacy and safety, including the statistical testing strategy and endpoint definitions.

Additionally, while within-arm genotype effects on outcomes will be critical to assessing the reliability of the sub-study cohort, our primary interest will be the randomized treatment comparison. We recommend that the outcome measures (safety and efficacy) for the pharmacogenomic analysis be the same as what you intend to test in the overall population of ENGAGE AF-TIMI 48.

You should conduct analyses that limit the analysis population to only those who provided consent and a sample at or prior to randomization to examine survival bias. Additionally, if participation in the DNA sub-study differed by geographic region/site, then please also present overall summary clinical characteristics and treatment effects for the participating sites.

Discussion at the Meeting
After presenting slide 4, Daiichi-Sankyo added that they conducted the sub-study globally, but because of local regulations, did not conduct the study in Brazil, Guatamala, Denmark, Thailand, and Turkey. When asked whether the Agency will review the statistical analysis plan (SAP) for the pharmacogenomics substudy prior to NDA submission, the Agency explained that ENGAGE AF-TIMI48 is designed to evaluate the effect of edoxaban using warfarin as the comparator on the pre-specified clinical outcomes. The Agency views the proposed pharmacogenomics analysis as exploratory with incomplete ascertainment of subjects' genotypes and no intent to develop a companion diagnostic. As stated in the preamble to the preliminary responses, genotypic variation in response to warfarin is already described in the warfarin label. The Agency did not express a need to review the proposed SAP for an exploratory study at this late stage. However, the sponsor can submit its SAP for the record. If the sponsor intends to pursue the pharmacogenomics statistical analysis plan, it will be a matter of review. Daiichi-Sankyo acknowledged the Agency's comments.

5. We believe that the effects of *VKORC1*/*CYP2C9* genotypes on warfarin metabolism are well established; however, we also anticipate that it may be difficult to observe a PGx effect on warfarin bleeds in a well-conducted clinical trial because the compliance with INR monitoring may be higher within the clinical trial than in routine clinical care. [i.e. *VKORC1* may have an effect on warfarin dose and other warfarin metrics (TTR, etc); (b) (4) Does the Agency agree?

FDA Preliminary Response

No. The absence of an effect in the warfarin group would raise concerns about the validity of the data source (e.g., lack of power, bias, confounding). It is plausible that edoxaban is not susceptible to the same genotype effects as warfarin although this is likely to be implicit based on the clinical pharmacology.

Discussion at the Meeting

Daiichi-Sankyo presented slides 6 and 7 and highlighted the questions that they hoped to answer with the sub-study data (see slide 7, attached as an appendix to these minutes). Dr. Pacanowski responded that the information could be valuable in understanding the role of *VKORC1*/*CYP2C9* genotypes on warfarin metabolism. He added that the Agency concern (b) (4) The Agency encouraged Daiichi-Sankyo to publish the data when available because that is likely to be the most appropriate mechanism to disseminate the information to clinicians. Another option would be an exploratory analysis, utilizing pop-PK, but even with exploratory analyses, a rigorous analysis plan was encouraged. (b) (4) .

6. If the subpopulation defined as 'warfarin sensitive' (i.e. carriers of *VKORC1* /*CYP2C9* variants) exhibits the same rate of bleeding with edoxaban therapy as the subpopulation without *VKORC1*/*CYP2C9* variants, (b) (4) Does the Agency agree?

FDA Preliminary Response

Please see introductory comments and response to Question 5.

Discussion at the Meeting

Please see discussion under question 5.

3.0 OTHER IMPORTANT INFORMATION

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues raised at the meeting that required further discussion.

5.0 ACTION ITEMS

There were no action items for either the sponsor or the Agency.

6.0 ATTACHMENTS AND HANDOUTS

The slides presented at the meeting are attached as an appendix to these minutes.

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/s/

ALISON L BLAUS
01/09/2013

RAJANIKANTH MADABUSHI
01/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77254

MEETING MINUTES

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for edoxaban (DU-176b).

We also refer to the meeting between representatives of your firm and the FDA on February 28, 2012. The purpose of the meeting was to discuss the format and content of your upcoming dossier.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us, in an official submission to the IND, of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Blaus, Regulatory Project Manager at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	28 February 2012 from 1:30 – 3pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 77254
Product Name:	edoxaban (DU-176b)
Indication:	Atrial fibrillation
Sponsor/Applicant Name:	Daiichi-Sankyo
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Alison Blaus

FDA ATTENDEES

* *Office of New Drugs, Division of Cardiovascular & Renal Products*	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Clinical Team Leader
Maryann Gordon, M.D.	Clinical Reviewer
Martin Rose, M.D.	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Patricia Harlow, Ph.D.	Pharmacology/Toxicology
Alison Blaus	Regulatory Health Project Manager
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D.	Team Leader
Divya Menon-Andersen, Ph.D.	Clinical Pharmacology
* *Office of Biostatistics*	
Steve Bai, Ph.D.	Statistician

SPONSOR ATTENDEES

**Daiichi-Sankyo Attendees*	
Howard Hoffman, M.D.	Vice President, Regulatory Affairs
Doreen V. Morgan, PharmD, MS	Executive Director, Regulatory Affairs
Sejal P. Emerson, PharmD	Associate Director, Regulatory Affairs
Howard Kessler	Senior Director, Regulatory Operations
Karen Frantz	Director, Regulatory Operations
Michele Mercuri, M.D., Ph.D., FAHA	Vice President, Clinical Development
Indravadan Patel, M.D.	Executive Director, Clinical Development
Michael Melino, MS, Ph.D.	Senior Director, Clinical Development
Reinilde Heyrman, M.D.	Vice President, Clinical Development
Karen S. Brown, Ph.D.	Executive Director, Clinical Pharmacology
Martins O. Adeyemo, Ph.D., DABT	Senior Director, Medicinal Safety
Youngsook Choi, M.D.	Senior Director, Clinical Safety & Pharmacovigilance
David Ramage	Senior Project Data Operations Manager
William Crerand	Director, Data Management
Minggao Shi, Ph.D.	Senior Director, Biostatistics

Frances P. Bessette	Director, Global Project Management & Leadership
Nigel Scott, Ph.D.	Director, Regulatory Affairs (UK)
Masafumi Yokota, DVM	Associate Manager, New Drug Regulatory Affairs (Japan)
** Consultant*	
Joshua Betcher, Ph.D.	Senior Statistical Scientist, Quintiles

1.0 BACKGROUND

Edoxaban (DU-176b) is an orally administered inhibitor of coagulation Factor Xa, being developed to reduce the risk of stroke and systemic embolic events (SEEs) in patients with atrial fibrillation (AF). The sponsor is conducting, in conjunction for TIMI study group, one pivotal Phase 3 trial (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 - **E**ffective a**N**ticoa**G**ulation with factor x**A** next **G**Eneration in **A**trial **F**ibrillation (**ENGAGE AF-TIMI 48**)".

TIMI 48 is an event driven trial but is anticipated to be completed and submitted as a NDA in 1Q 2013. The meeting on 28 February 2012 was scheduled to discuss the format and content of this planned dossier as well as any additional requests from the Agency based on their experience with competitor products. Slides presented at this meeting can be found as an appendix to these minutes.

2. DISCUSSION

2.1. Questions for the FDA

Non-clinical

1. Does the Division agree that the proposed nonclinical package is adequate for filing the NDA?

   FDA Preliminary Response
   Yes.

   Discussion at the Meeting
   No further discussion.

2. Does the Division agree that the studies conducted to qualify D21-2393, a human specific metabolite, are adequate for filing the NDA?

   FDA Preliminary Response
   Yes.

   Discussion at the Meeting
   No further discussion.

3. Does the Division concur with the Sponsor's proposal to submit the tumor datasets in SAS transport (.xpt) file format in the NDA?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

Clinical Pharmacology

4. *In vitro* Studies
    a. Does the Division agree that in vitro ADME studies with human and other biomaterials conducted by the Sponsor are sufficient for NDA filing?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

    b. Does the Division agree with the Sponsor's proposed placement of the discussion of in vitro pharmacology studies with human biomaterials in Module 2.4 (Nonclinical Overview) and 2.6.2 (Pharmacology Written Summary)?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

5. Clinical Pharmacology Summary
    a. Does the Division agree that this clinical pharmacology package is adequate for NDA filing?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

    b. Does the Division agree with the proposed topics for discussion in Module 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods) and Module 2.7.2 (Summary of Clinical Pharmacology Studies)?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

6. Does the Division concur with our proposal, for Phase 1 studies, to submit CRFs for deaths, subjects who discontinued due to adverse events, or subjects who had an SAE?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

7. Does the Division concur with our revised proposal for the presentation and summarization of data for the active metabolite, D21-2393, in the ENGAGE AF-TIMI 48 CSR?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

8. Does the Division concur with the Sponsor's proposal to provide data on the (b) (4) of edoxaban anticoagulation by PCC based on a healthy volunteer PK/PD study?

FDA Preliminary Response
The adequacy of a PK/PD study to support the use of a (b) (4) will be dependent on (b) (4)

Additionally, how do you propose to determine the doses of the (b) (4) to be studied?

Discussion at the Meeting
Daiichi-Sankyo, in slide 21, asked if the information requested could be provided at the time of filing. The Agency said that the sponsor's proposal was acceptable if the review is classified as standard. If the review is classified as priority, then the information would need to be included in the initial NDA submission. The sponsor said that they would then plan for inclusion in the initial submission.

The sponsor, in slide 22, provided some information regarding the dose of a (b) (4) studied (data submitted with the initial IND). The Division, however, said that it would be difficult to include any information in the label without clinical outcomes data in the intended population. Dr. Stockbridge asked if the sponsor had any information about the use of (b) (4) from the Phase 3 trial (ENGAGE. The sponsor indicated that they would review the data when they become available.

9. Pharmacometrics
    a. Does the Division concur with the pharmacometric analyses proposed for inclusion in the NDA?

FDA Preliminary Response
Yes. Also, please refer to our advice letter dated February 13, 2012.

Discussion at the Meeting
No further discussion.

b. Does the Division concur with the proposal above for the presentation of the pharmacometric analyses?

FDA Preliminary Response
Yes. Also, please refer to our advice letter dated February 13, 2012.

Discussion at the Meeting
No further discussion.

NDA Summary Documents in Module 2

10. Does the Division concur with the Sponsor's proposed categories for integration of safety data in the summary of clinical safety (Module 2.7.4)/ISS?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

11. Does the Division concur with the proposed format for Module 2.7.4?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

12. Does the Division concur with our proposal for presentation of the clinical safety data for the Phase I clinical pharmacology studies?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

13. Does the Division concur that the previous responses to the above questions regarding Module 2.7.3 and Module 2.7.4 have not changed?

FDA Preliminary Response
Summaries belong in Module 2 and analyses belong in Module 5, section 5.3.5.3. The ISS text and data should be placed in m5.3.5.3, not 5.3.5.1. Please refer to "Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB)", located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

Discussion at the Meeting
The sponsor clarified their plan (please see slides 3 – 5 attached as an appendix to these minutes); the ISS narrative will be in Module 2 and the ISS tables, listings, and figures in Module 5. The also noted that they will provide hyperlinks between both Modules. After further consideration with the Division, the sponsor agreed to put the ISS for Phase I and II studies in Module 2 and all information for the Phase 3 trial in Module 5.

Clinical (ENGAGE AF-TIMI 48, Phase 2 AF, Phase 2/3 DVT)

14. Does the Division concur with the proposal that key primary efficacy variables and key secondary efficacy variables captured as potential efficacy endpoints will be presented under efficacy results only and will not be presented in the safety results?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

15. Does the Division concur with the above proposal for data presentations of the safety events with separate tables for bleeding AEs, nonbleeding safety, and safety events of interest without inclusion of any investigator reported suspected efficacy endpoint events?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

16. Does the Division concur with the proposal for inclusion of CEC and DMC meeting agendas, minutes, etc in Appendix 16.1.9 of CSR?

FDA Preliminary Response
Yes. Please appropriately bookmark each item so that the reviewer can easily navigate between and within each item.

Discussion at the Meeting
No further discussion.

17. Does the Division concur with the proposal to submit CRFs for deaths, discontinuations due to AEs, and SAEs in the Phase2 AF and Phase 2/3 DVT studies?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

18. Does the Division concur with the proposal to submit CRFs for deaths, discontinuations due to AEs, withdrawals due to AEs, SAEs, and adjudicated events in the ENGAGE AF-TIMI 48 study?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

19. Adjudication Packages
    a. Does the Division concur with the proposal to submit the prespecified adjudication packages for the above listed studies?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

    b. Does the Division concur with the proposal to position a subject's CEC Adjudication Package after the subject's corresponding eCRF in the respective CSRs for the ENGAGE AF-TIMI 48 and PRT018 studies?

FDA Preliminary Response
Yes. Please include each adjudicator's assessment and the final adjudication after the adjudication packages, as well as the investigator's assessment of each event. Please use appropriate bookmarking within this section to facilitate review.

Discussion at the Meeting
No further discussion.

20. Patient Narratives
    a. Does the Division concur with this revised proposed format for Patient Narratives?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

    b. Does the Division concur with the proposal to receive narratives for permanent discontinuations due to an AE as defined above?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

21. Does the Division agree with this navigation schema?

FDA Preliminary Response

Yes. Please submit a SAS dataset that includes all randomized subjects (one line of observation per subject) and identifies subjects with submitted CRFs, narratives, adjudication packages, and expert hepatologists' causality assessments.

Discussion at the Meeting

No further discussion at the meeting.

22. Does the Division concur with the proposal to submit only these listings in the ENGAGE AF-TIMI 48 CSR?

FDA Preliminary Response

Yes. Please submit SAS datasets for listings #1 (Unblinded subjects while on treatment and during the ITT period), #4, #5 (include the study drug lot number, container number and date dispensed for each subject during the entire study), #25 (should include unique subject ID, date of event, each hepatologists' assessment and the final assessment of causality), and #28.

Discussion at the Meeting

No discussion at the meeting.

23. Does the Division concur with the proposal to submit SDTM datasets only and not individual patient data listings?

FDA Preliminary Response

Yes. Please use CDISC SDTM format, version 3.1.2, including the Amendment 1 variables in the parent domains.

Discussion at the Meeting

No further discussion.

24. Does the Division agree with the placement of the quality oversight documentation as an addendum to the ENGAGE AF-TIMI 48 Clinical Study Report?

FDA Preliminary Response

Yes. Please provide sufficient detail to allow a ready understanding of trial conduct.

Discussion at the Meeting

No further discussion.

25. Does the Division concur with this proposed approach for counting protocol violations in the summary level clinical site data for ENGAGE AF-TIMI 48?

FDA Preliminary Response

Yes.

Discussion at the Meeting

No further discussion.

Confirmation of Types and Format of Clinical Datasets

26. Does the Division concur with the proposed Format/Type of the Clinical Pharmacology and clinical datasets?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

27. Does the Division concur with the proposed formats for the pharmacometric datasets?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

28. Does the Division concur with the Format/Type of the above described analysis data sets that will be submitted?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

Additional Topics for Discussion

29. Does the Division concur with NDA filing plan to 1) request priority based on results of the ENGAGE AF-TIMI 48 study and 2) request for a "rolling submission" for Modules 3 and 4, and as resources allow, commit to commence the review of Modules 3 and 4 at the time of their submission based upon an agreed upon schedule?

FDA Preliminary Response
The decision for a priority review will be determined at the time of filing of the dossier. Priority reviews are granted when the preliminary assessment of a drug indicates that that it may be a significant improvement compared to marketed therapies, e.g., more effective or less toxic. The request for a "rolling submission" will be addressed once the data from the ENGAGE-AF-TIMI 48 trial are presented at your topline meeting

Discussion at the Meeting
No further discussion beyond the Division's preliminary response.

30. Does the Division concur with our proposal to request a waiver in AF for pediatric patients for the above stated reason?

FDA Preliminary Response
Your request for a waiver will be reviewed by the Pediatric Review Committee (PeRC) once your NDA is submitted, but the Division agrees that a waiver would be appropriate.

Discussion at the Meeting
No further discussion.

31. Does the Division agree with the Sponsor's proposal for a (b) (4) for these studies?

FDA Preliminary Response
Financial disclosures must be submitted for all trials pertinent to the approval of your application.

Discussion at the Meeting
The sponsor clarified that they will include financial disclosure information for the Phase 3 trial (TIMI 48) and the dose ranging study (018), but did not plan on providing disclosure for any other study. The Division said that this was acceptable.

32. Regarding the information required in 21 CFR 312.120 does the Division concur that the previous response to the above question has not changed?

FDA Preliminary Response
Yes, it has not changed.

Discussion at the Meeting
No further discussion.

33. Does the Division agree with our proposal to include literature references cited in Module 2 summary documents only?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

34. Does the Division concur with our proposal not to submit SPL with the initial NDA submission?

FDA Preliminary Response
No. The submission of SPL is required for filing.

Discussion at the Meeting
No further discussion.

35. Does the Division concur with our proposed safety cut-off date (for ongoing studies and post marketing data from Japan) for the NDA?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion.

2.2. Additional FDA Requests

Datasets for Efficacy Analyses

- Include a dataset containing multiple records per subject randomized to warfarin and the following information: the unique subject id, site id, date of INR measurement, value of INR, indicator of whether or not the subject was on warfarin at the time of INR measurement, indicator for whether a subsequent dose adjustment was made (increased, decreased, no change).

  Discussion at the Meeting
  As discussed in slide 8 and 9, the sponsor can provide the above outlined dataset, but said that they will not be able to provide an indicator for whether the dose was changed. The sponsor did point out, with the example on slide 9, that the last three warfarin doses and the subsequent INR will be provided and a change can be noted if comparing the doses of one month to the next. In addition, the sponsor said that they would add date to the dataset to help in the Division's analyses. Dr. Grant asked how dose adjustments not made by the investigator, but by another physician for an SAE for example. The sponsor said that the details would be captured in the narrative of the SAE, but the dose adjustment detailed in the dataset.

- In addition to the INR data for warfarin subjects, the Division also requests all INR data for edoxaban subjects. The sponsor agreed to provide the INR data for edoxaban treated subjects in the dossier. Please provide the data supporting a relationship between edoxaban and Factor Xa assays.

  Discussion at the Meeting
  Please see slides 21 and 23, attached as an appendix to these minutes. Dr. Madabushi added that the data regarding the PK/PD modeling for edoxaban, PT and bleeding and the data supporting the relationship between edoxaban Factor Xa assays would need to be provided at the initial submission. Dr. Madabushi recommended that the PK/PD report based on Phase 3 data be submitted with the initial submission.

- Include a dataset containing one record per subject randomized to warfarin and the following information: unique subject id, site id, VKA experienced (yes or no), duration of time in study (days), duration of time (days) on study medication (excludes periods of medication interruptions), number of INR measurements made during/as part of study, maximum number of days between two consecutive INR measurements while subject was on study medication, start date for that period (i.e., date of INR measurement beginning that period), end date for that period (i.e., date of INR measurement ending that period).

  Discussion at the Meeting
  Please see discussion under bullet 8 of the "Additional FDA Requests" subsection, "Other Requests".

- Include a dataset containing multiple records per subject randomized to warfarin in ENGAGE and the following information: unique subject id, site id, country, region, and the % time in range, % time below range, and % time above range for the following INR ranges: 2-3 and 1.5-4. The percentage of

time in, above and below a given range should be calculated for the following study time periods for each subject: <1 month, ≤ 3 months, ≤ 6 months, ≤12 months and overall.

The time in these ranges should be calculated in two ways as specified below:

- Time in therapeutic range excluding warfarin treatment interruptions (TTRE): The evaluation of a patient's compliance to warfarin during treatment period should be assessed by the % of days when the INR is in the required range. A linear interpolation using the Rosendaal method should be performed. A linear equation should be fitted using the actual measured INR values. After the linear equation is fitted, a value will be substituted for each day when the patient took study medication and did not have an actual INR measurement. For patients who had temporary discontinuation of study warfarin, the time interval between temporary discontinuation and restart of medication should not be counted. Exclude INR values measured during the first week of randomization.
- Time in therapeutic range including warfarin treatment interruptions (TTRI): calculation as above, but include periods of temporary discontinuation of study warfarin (i.e., interpolate as if no interruption had occurred).

We also request that you provide the SAS code used to create this dataset along with the base data set and any intermediate datasets used.

Discussion at the Meeting

In slide 10, the sponsor agreed that they would be able to provide the TTRE as described in the preliminary comment, including any interruptions, but with a small adjustment. The sponsor's on treatment (OT) analysis will also include INR data while on treatment but also 3 days after treatment ended. The Division noted that that would be acceptable, but also mentioned that without the three days would be ideal to have as well. The sponsor agreed to provide both.

Regarding the intermediate datasets, the sponsor agreed and will provide. SAS codes were discussed under bullet 3 of "Other Requests" section.

- Please include a dataset (subjects who permanently discontinued study medication only) containing one record per subject and information on whether or not the subject was treated with an anticoagulant following study medication discontinuation, and if so, what anticoagulant was used. If this information is contained in another dataset in the specified format, a separate dataset does not need to be submitted. Please reference the name of this data set in your submission.

Discussion at the Meeting

Please see slide 11 in the appendix. As noted, the sponsor did not capture other anticoagulant use (with the exception of warfarin) on the eCRFs for those patients who discontinued treatment. The sponsor explained that patients were seen for monthly INR visits after discontinuation, but would only capture other concomitant medication information if the patient had an adverse event (AE). For those discontinued patients with an AE, the sponsor captured on the CRFs the previous 30 days of concomitant medication use. On a related note, the Division asked the sponsor to define in the protocol the definitions of "discontinuation" and "interruptions". Per the Division, the term "discontinuation" should be used only for subjects that never restarted study drug, and the term "temporary interruptions" (not "temporary discontinuations") should be used for subjects who stopped treatment for a period of time, but then restarted treatment.

Dr Rose asked the sponsor how subjects were transitioned to proper anticoagulation at the end of the study. The sponsor explained that all events would be counted to a common study end date plus the

time between that end date and the patient's final visit (within 90 days). Dr. Grant added that the sponsor committed to "minimal investigator discretion" as to when each subject will undergo the final visit, with the details made explicit in the protocol. The sponsor further explained that patients would be followed for safety events, via phone, 30 days after the final visit (± 7 days). The sponsor agreed to provide the specific questions that would be asked of the patients in these "virtual" telephone visits. If the patient had an event (per the telephone call), then the patient was to be brought back to the site for an on-site visit. At that visit, information regarding the event, concomitant medications and other standard assessments would be obtained. These events would be adjudicated.

In a related discussion, Dr. Rose asked how INRs were obtained in the trial, specifics regarding sham INRs, and if there were any limitations to the point-of-care (POC) device. The sponsor said that there was a 6-digit limit to the POC device. The sponsor said that they would provide information regarding the sham INRs in their initial NDA submission. Dr. Rose explained that in the submission, there should be a dataset that includes the actual INR and what was reported to the site.

Datasets for Safety Analyses

- Please include a dataset containing all subjects treated and the following information: one record per bleed event and the following information: the unique subject id, treatment received, study termination date, first medication date, last medication date, type of bleed event (example, "major" by protocol definition), major bleed event number for subject (multiple events on the same day should be counted as one event), event date, event days from first dose, indicator for adjudicated as major bleed, indicator for investigator reported major bleed, indicators for location of EACH critical organ bleed (example, indicator for GI bleed, indicator for intracranial bleed), indicator for hemoglobin drop of = 2 g/dL, indicator for hemoglobin drop of = 5 g/dL, indicator for = 2 U transfusion, indicator for = 4 U transfusion, indicator for bleeding associated with hypotension requiring intravenous inotropes, indicator for requiring surgical intervention to stop bleeding, indicator for bleeding requiring hospitalization, indicator for bleeding resulting in death, indicator for event occurring on treatment, indicator for event occurring post treatment +30 days, indicator for event occurring greater than 30 days off treatment.

  Type of bleed event should include protocol defined events (including hemorrhagic stroke, ICH), and major GI bleed, fatal bleed, ISTH major bleed, and GUSTO severe bleeding.
  Subjects without an event should be censored at the time of last information collected on the major bleed event. This data set should be set up to allow time to event analyses for all adjudicated events.

  Discussion at the Meeting
  As detailed in slides 12 and 13, the Division's request asked for an "indicator for investigator reported major bleed", but the sponsor explained that they did not capture the investigator's assessment of the severity of bleed (e.g., major, etc). Daiichi noted events were identified for bleeding adjudication two ways. Either the investigator completed the "bleed CRF" or by a programmatic check of the laboratory and AE data. If the CRO's programmatic check identified a possible major bleed that was not identified by the investigator, then the CRO sent a query to the site to review the event. The investigator could decide to either complete the bleed CRF or reaffirm that the event was not a significant bleed. The completion of the bleed CRF triggered adjudication. Dr. Beasley asked the sponsor to include the following in the dataset: type of investigator reported bleed (determine programmatically by using the investigator provided information on the bleed CRF), and an indicator for how the bleed was identified (i.e., investigator, programmatic, or investigator assessed as no event after a query). The sponsor agreed.

In a related discussion, Dr. Grant asked if adjudicated events were reviewed in "real time" or if there was a lag between trigger and review. The sponsor noted that there was an average of 60 days between sending an event for adjudication and its review by the committee. Dr. Grant asked about how much time elapsed between investigator reported events and submission of data about events to the DSMB. Daiichi stated that the DSMB was reviewing events in "real time" for both efficacy and safety. Dr. Grant then noted that the sponsor must have had some method for identifying bleeds as probably major based on information supplied by the investigator to avoid having to wait for the results of adjudication. The sponsor indicated they did supply information to the DSMB about major bleeds based information from the investigator. Dr. Grant requested the information supplied to the DSMB be included in the NDA and the sponsor agreed.

- A dataset that contains multiple records per randomized subject and the following information: the unique subject id, treatment arm, indicator flag for treated subjects, randomization date, study termination date, first medication date, last medication date, the following liver test results, ratios, and date of collection: ALT, AST, total bilirubin, and alkaline phosphatase, and an indicator for central or local lab. All liver test results should be in consistent units. Note that there is a date associated with each lab test, e.g., ALT_date, AST_date.

  Discussion at the Meeting
  No further discussion.

- A dataset that contains multiple records per subject and the following information: the unique subject id, treatment arm, the date and results of all laboratory tests done to rule out other causes of drug induced liver injury.

  Discussion at the Meeting
  No discussion at the meeting.

Other Requests

- Please submit all SAS codes used and all data sets used. For example, if a SAS code contains a macro, please include the macro code.

  Discussion at the Meeting
  The sponsor agreed. This information will be included in the table discussed under bullet 3 of this section.

- Please submit MedDRA coding dictionaries for bleeding related AEs, hepatic related AEs, and any other significant AEs for edoxaban as SAS transport files.

  Discussion at the Meeting
  Dr. Beasley clarified that this request is limited to the preferred terms used for coding during the P3 trial (ENGAGE).

- Please submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the NDA. The table should contain the following:

  - title of the table or figure in NDA

- a hyperlink to the location of the table or figure with page number
- a hyperlink to the SAS code used to create the table or figure

Discussion at the Meeting
During the meeting, the request above was refined to request a table of the tables and figures featured in the main Clinical Study Report for the pivotal Phase 3 trial. Dr. Beasley also added that the SAS codes should also include any macros used to create that table or figure. Upon further discussion, the sponsor also agreed to add the following item to the table:

- names of the datasets used to create the table or figure (a hyperlink would be useful, but not necessary)

The Division and the sponsor agreed that it was appropriate to place this table in Module 2 (Clinical Overview).

- An adjudication dataset should be submitted that contains one line per event and the event type being adjudicated (i.e., stroke, major bleed, etc.), what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the nature of the event, each adjudicators' result (in chronological order)and date of adjudication, final adjudication result, the study number, unique subject id, treatment arm, and date of event.

Discussion at the Meeting
No discussion at the meeting.

- Please provide sample clinical trial kits, identical to those used during ENGAGE. One kit from the warfarin arm and another from edoxaban should be provided to Ms. Blaus' desk address.

Discussion at the Meeting
No further discussion.

- Please provide a dataset(s) for time to event (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Include whether censoring was determined by a patient visit or by telephone call. This data set should allow one to analyze by ITT as well as on-treatment. The events should include all adjudicated events and any important composite endpoints.

Discussion at the Meeting
No discussion at the meeting.

- Please include Steering Committee and DSMB meeting minutes (including any data/slides presented to the Committee). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the edoxaban clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

Discussion at the Meeting
The sponsor agreed to provide all of the above for the Steering Committee, DSMB, and any other "Leadership Committees" detailed in the protocol that convene to discuss ENGAGE.

- In addition to the "subgroups of interest for efficacy assessments" identified in your SCE SAP, efficacy findings should also be provided for the following subgroups: prior VKA use, aspirin use at baseline, clopidogrel use at baseline, type of atrial fibrillation and findings in the U.S. CHADS2 scores should be broken down into the following groupings: 0, 1, 2 and ≥3.

  Discussion at the Meeting
  On slide 14, the sponsor asked if their definition of "VKA experienced" was acceptable. The sponsor did not collect information to define "VKA experienced" differently. Dr. Beasley said that "VKA experienced" as defined in the trial was acceptable.

- Please provide the following information relevant to the assessment of (1) deaths, (2) primary efficacy endpoint events and (3) primary safety endpoint events occurring after the discontinuation of study drug:
  - Rates of these events (with HR and 95% CIs) over the 30 days after the last dose of study drug, with separate tables for patients who discontinued study drug early and those who completed the study. The tables for these events should also include event rates during segments of the 30 day post discontinuation period: days 1-7, 8-14, and 15-30 .
  - For these tables, provide listings of patients who had events with: Patient number, type of event, age, baseline CHADS2 score, history of prior stroke/TIA/SE (yes/no), date and relative day of event (1-30), and any anti-coagulant or anti-platelet medication received during the post-treatment period with dates, dose and INR information
  - Provide information by arm on post-treatment use of anticoagulant or antiplatelet drugs for early d/c pts and completers, with post treatment event rates for patients who did or did not take each class of medications.
  - Provide information on # and percent of patients who received the blinded transition kit. Provide 30 day post treatment event information for those who did and did not receive the blinded kit. For this analysis only:
    - For edoxaban arm patients who received the blinded transition kit, day 1 of the 30 day post treatment period is the day after the kit was dispensed.
    - For edoxaban arm patients who did not receive the kit, day 1 is the day after the last dose of study drug
  - For all other patients and all other post treatment analyses, day 1 is the day after the last dose of active study drug.

  Discussion at the Meeting
  As noted in slide 15, regarding "last dose of study drug" under sub-bullet one, the sponsor asked how the Division would like to treat interruptions in therapy. Dr. Rose noted that capturing this data in addition to those data during the transition period would be helpful. He did add that distinguishing the two would be helpful. The sponsor referred to the discussion under bullet 5 of "*Datasets for Efficacy Analyses"* noting what data would be available and under which circumstances. Therefore, some of the information under the sub-bullets above would be impossible to obtain should the patient not have an event between the last visit and the telephone follow-up. Dr. Rose noted that this was fine.

- A description of the responsibilities of each ARO or CRO used in ENGAGE.

  Discussion at the Meeting
  No further discussion.

- Please provide all versions of your clinical trial monitoring plan for ENGAGE.

  Discussion at the Meeting
  The sponsor agreed to provide all versions.

- Please provide all versions of your detailed data management plan, including both manual and programatical data checks used throughout the study.

  Discussion at the Meeting
  The sponsor agreed.

- Please provide a detailed description of how study drug was packaged and maintained at the study sites, as well how drug was dispensed to patients. Were kits or medication bottles dedicated in advance to individual patients? How were dispensing and drug return records created and maintained? Also, describe in detail your methodology for detecting medication errors during and after the study, monitoring for such errors and any corrective actions taken with regard to medication errors.

  Discussion at the Meeting
  No further discussion.

- Attached as an appendix to these preliminary responses is an information request provided by the Office of Scientific Investigations (Appendix I). This document includes data requests that are to be addressed in your initial submission. [This request appeared in the preliminary comments dated 27 February 2012. Please refer to those preliminary responses to obtain the attached referenced here].

  Discussion at the Meeting
  No further discussion.

- Also attached to these minutes is the Clinical Pharmacology Review Aid (Appendix II). Please refer to this document when putting together clinical pharmacology information in your dossier. [This request appeared in the preliminary comments dated 27 February 2012. Please refer to those preliminary responses to obtain the attached referenced here].

  Discussion at the Meeting
  No discussion at the meeting.

- Liver Data: Separate from the primary efficacy and safety datasets, additional datasets will need to be provided according to the specifications provided in an email to Doreen Morgan on 17Feb12. Please provide these in the original submission

  Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hy's Law" cases of elevated ALT or AST >3xULN and TBL >2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings. This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug- related liver injury (DILI) be made. Liver biopsy is not definitive, and

there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL >2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH system, as used by medical reviewers at CDER, includes the capability to create time-course graphs for each subject, and to read the narrative summaries, helping them in drawing their own conclusions as to whether the drug may have caused the abnormal findings. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives be written by *physicians or other medical personnel* skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

Discussion at the Meeting
Per slide 18, the sponsor reviewed OSE's EDISH requirements and only agreed to provide those narratives listed. The only circumstance where a narrative requested would not be provided, would be "Isolated ALT >5x ULN or TBL >2x ULN". Dr. Stockbridge confirmed that this was acceptable.

- ***Additional Request During Meeting:*** Unblinding – Dr. Grant asked the sponsor to include in their submission a list of all subjects unblinded during the trial (ENGAGE), regardless of the reason for unblinding. Please put these subjects in a dataset (using their unique subject ID) and include the reason for unblinding.

2.3. Post Meeting Requests

1. Please provide an encrypted (e.g., with WinZip) copy of the randomization list. This should be submitted to the IND as soon as possible. The key to the randomization list should be submitted with the NDA submission.

   Post-Meeting Note:
   The encrypted randomization list for ENGAGE was already submitted to the IND in your submission dated November 11, 2008.

The following requests can be submitted any time between the receipt of these minutes or with the briefing book for the top-line results meeting:

2. Request that all data in the eCRF system be submitted in the SAS transport files regardless of whether the sponsor considers them to be "CRF" data, e.g., status fields, monitor notes are very helpful in evaluating site quality. Submitting all data in the eCRF may require deviating significantly from CDISC SDTM because SDTM does not define explicitly many CRF variables and the domains into which they should be placed.

3. Request submitting the audit trail of the eCRF system in a SAS transport file.

4. Request a SAS transport file providing the original and final investigator verbatim terms, as well as deleted terms, for all adverse events. If investigator verbatim terms for endpoint events are used for

triggering or referring events for adjudication, provide SAS transport files with the original and final investigator terms for them as well.

5. Reaffirm that the CRFs must include all clinical documents collected regarding the patients regardless of whether the sponsor labels them CRFs, e.g., Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.

6. Request submitting CRFs for all discontinuations of therapy, including withdrawals of consent, regardless of the assigned reasons for withdrawal.

7. Clarify that the sponsor should submit all adjudication packages exactly and completely as seen by the adjudicators, including all source documents and query results. If adjudication packages were prepared but not sent to the CEC, please submit all of them. We do not understand what the "pre-specified" or "protocol-specified" adjudication packages are. Simply put, if the CEC saw it or anybody prepared it, we'd like to see it.

3.0 OTHER IMPORTANT INFORMATION

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The sponsor agreed to provide the questionnaire to be used at the close out of the study for the follow-up "virtual" telephone visits.	Sponsor	Prior to finalizing the questionnaire. Please leave for adequate time for review.

5.0 ATTACHMENTS AND HANDOUTS

Please find attached to these minutes, the slides that were presented by the sponsor at the February 28, 2012 meeting.

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/s/

NORMAN L STOCKBRIDGE
03/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77254

ADVICE LETTER

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for edoxaban (DU-176b) Tablets.

We also refer to your amendment dated June 1, 2011, containing a request for advice regarding your planned NDA filing for edoxaban.

Upon review of the above mentioned document, we have the following responses to your questions:

1. Does the Division concur with our proposal to provide (b) (4) narratives for all patients in the ENGAGE AF – TIMI 48 study who died, had a Serious Adverse Event, who permanently discontinued study drug due to an adverse event, had an event that required adjudication according to the protocol/CEC Charter, or had an event of special interest in place of the standard written narrative format?

   FDA Response
   No. Based on the sample narrative provided, it is unlikely that the narratives (b) (4) will facilitate review. We recognize the difficulty of generating a large number of narratives (you report that the number would be upwards of 21,000). Alternatively, we request you submit higher quality narratives, drafted and reviewed by physicians or other medical personnel, for a more limited number of events. Please provide narratives for "Deaths" and "Discontinuations due to an adverse event". "Discontinuations due to an adverse event" should also include those patients who withdrew their consent due to an adverse event. Narratives for safety and efficacy end points or discontinuations due to an endpoint event do not need to be provided as these events would have a corresponding adjudication packages that you will be providing. Please also note that you should be prepared to furnish to the FDA, in an expedited manner, other narratives upon request during review of the NDA.

2. Does the Division concur with the DSPD proposal to split the presentation of safety data across Module 2 and Module 5, with the narrative portion located in Module 2.7.4 and the appendices of tables, figures, and datasets located in Module 5.3.5.1 (for ENGAGE AF) Module 5.3.5.3 (for integrated Phase 1 and 2 data)?

   FDA Response
   Yes.

3. Does the Division concur with our proposal to provide a summary of key efficacy data from the ENGAGE AF study only in Module 2.7.3 and provide a hyperlink to the appropriate appendices of tables, figures, and datasets in the ENGAGE AF clinical study report in Module 5.3.5.1?

   FDA Response
   Yes.

4. Since these studies were conducted under GCP, the principles of the Declaration of Helsinki, and in accordance with the laws of the country in which the study was conducted, per 21 CFR 312.120(c), will the FDA grant a waiver for inclusion of certain supportive information required in 21 CFR 312.120(b) for the above listed foreign clinical studies not conducted under an IND in the EU, China, or Japan?

   FDA Response
   We agree, providing that these studies do not contribute materially to your application.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening adverse experiences associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];

- Reporting any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, in writing to this Division and to all investigators within 15 calendar days after initial receipt of this information [21 CFR 312.32(c)(1)]; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, please contact, Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ALISON L BLAUS
08/22/2011

NORMAN L STOCKBRIDGE
08/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063266

MEETING MINUTES

Daiichi Sankyo, Inc.
Attention: Sandra Smith, R.Ph., M.B.A.
Senior Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Ms. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Edoxaban Tablets (DU- 176b).

We also refer to the meeting between representatives of your firm and the FDA on May 13, 2011. The purpose of the meeting was to obtain the Agency's feedback on the adequacy of the Sponsor's Phase 3 program to support their proposed indication: "Edoxaban is indicated for the [redacted] (b) (4)

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tyree Newman, Regulatory Project Manager at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Kathy Robie-Suh, M.D., Ph.D.
Clinical Team Leader, Hematology
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes, Meeting Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 13, 2011 / 3:00 – 4:00 PM
Meeting Location:	White Oak, Building 22, Room 1311
Application Number:	IND 063266
Product Name:	Edoxaban
Indication:	(b) (4)
Sponsor/Applicant Name:	Daiichi Sankyo, Inc.
Meeting Chair:	Ann T. Farrell, M.D.
Meeting Recorder:	Tyree Newman, B.S.

FDA ATTENDEES

Ann Farrell, M.D., Director (Acting)
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
George Shashaty, M.D., Clinical Reviewer
Tyree Newman, B.S., Regulatory Health Project Manager
Joseph Grillo, Pharm.D. Clinical Pharmacology Reviewer
Hari Cheryl Sachs, M.D., Medical Team Leader, PMHS
Alexander Putman, Ph.D., Pharmacologist
Matthew Bacho, Senior Regulatory Health Project Manager, PMHS
Nitin Mehrotra, Ph.D., Pharmacometrics, OCP
Qing Xu, Ph.D., Biostatistics Reviewer
Mark D. Rothmann, Ph.D., Biostatistics Team Leader

SPONSOR ATTENDEES

Sandra Smith, R.Ph., M.B.A. Executive Director, Regulatory Affairs
Howard Hoffman, M.D., Vice President, US Regulatory Affairs
Helene Petitjean, M.D., Director, Clinical Development
Jeanne Mendell, Ph.D., M.P.H., Director, Clinical Pharmacology
Michele Mercuri, M.D., Ph.D., FAHA, Vice President, Clinical Development
Minggao Shi, Ph.D., Senior Director, Biostatistics
Prof. Giancarlo Agnelli, M.D., Study Chairman

1.0 BACKGROUND

Daiichi-Sankyo requested a Type B meeting on March 18, 2011, to obtain the Agency's feedback on the adequacy of their Phase 3 program to support the proposed indication: (b) (4) On March 24, 2011, the Division sent Daiichi-Sankyo the meeting request granted letter.

On May 6, 2011, the Division emailed Daiichi-Sankyo preliminary responses to the questions contained in the meeting information package dated May 13, 2011.

2. DISCUSSION

(b) (4)

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(b) (4)

[redacted]

Discussion: **No discussion.**

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion]

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
N/A	FDA	N/A
N/A	Sponsor	N/A

5.0 ATTACHMENTS AND HANDOUTS

The Sponsor distributed the attached slides during the meeting. The Sponsor's responses in slides 1 through 8 were discussed during the meeting as reflected in the comments above. Slides 9 through 20 were not discussed or reviewed by the Agency.

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/s/

KATHY M ROBIE SUH
05/27/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 63,266

Daiichi Sankyo, Inc.
Attention: Sandra Smith, R.Ph., M.B.A.
Senior Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DU-176b Tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 29, 2009. The purpose of the meeting was to discuss the adequacy of your Phase 3 program to support the proposed indication: (b) (4) treatment (b) (4) of (b) (4) venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 29, 2009
TIME: 10:00 AM – 11:30 AM EST
LOCATION: White Oak Campus, Building 22, Conf. Room 1309
APPLICATION: IND 63,266
SPONSOR: Daiichi Sankyo, Inc.
DRUG NAME: DU-176b

TYPE OF MEETING: End of Phase 2, (Type B)

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
George Shashaty, M.D., Clinical Reviewer
Ronald Honchel, Ph.D., Pharmacology/Toxicology Reviewer
Diane Leaman, Safety Regulatory Project Manager
Lucie Yang, M.D., Clinical Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ PHARMACOMETRICS STAFF

Nitin Mehrotra, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL ATTENDEES:

DAIICHI SANKYO, INC

Youngsook Choi, M.D., Senior Director, Risk Management

Bruce Dornseif, Ph.D., Vice President, Biostatistics and Data Operations
Gretchen Golikov, B.S., MBA, Associate Director, Regulatory Affairs
Hazel-Anne Griffiths, Ph.D., Executive Director, EU Regulatory Affairs
Howard Hoffman, M.D., Vice President, US/EU Regulatory Affairs
John Kappelhof, B.SC., M.B.A., Director, Global Project Management
Satoshi Kunitada, Ph.D., Vice President, Project Leadership
Jeanne Mendell, Ph.D., M.PH., Director, Clinical Pharmacology
Michele Mercuri, M..D, Ph.D., FAHA,Vice President, Cardiovascular Clinical Development
Francis Plat, M.D., Vice President, Clinical Development
Lee R. Schwocho, Ph.D., Senior Director, Clinical Development
Minggao Shi, Ph.D., Senior Director, Biostatistics
Sandra Smith, R.Ph., M.B.A., Senior Director, Regulatory Affairs
Robbert Van Kranen, M.D., MFPM, M.B.A., Senior Director, Clinical Development
Hamim Zahir, Ph.D., Associate Director, Clinical Pharmacology

CONSULTANTS

(b) (4) — Study Chairman
Study Steering Committee Member
Study Steering Committee Member

BACKGROUND:

In a letter dated February 27, 2009, Daiichi Sankyo, Inc. (Daiichi) requested a meeting to discuss their proposed Phase 3 program. In a submission dated March 26, 2009, Daiichi submitted the meeting background package. On April 28, 2009, FDA sent Daiichi, via e-mail, draft responses to the questions raised in the March 27, 2009, background materials (See questions and responses below). FDA had additional points of emphasis that were not included in the draft responses but were stated in the meeting (see note below).

MEETING OBJECTIVES:

To discuss Daiichi's proposed Phase 3 program to support the proposed indication: (b) (4) treatment (b) (4) of (b) (4) venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE).

DISCUSSION POINTS:

Daiichi presented slides (see Daiichi slides below).

Slides 1-14 (Question 2)

Daiichi acknowledged a minor bleeding imbalance but noted that the study was not the best to characterize the bleeding profile of DU-176b. They noted that the 30 mg and 60 mg doses differ in the incidence of bleeding but are both expected to be less than that of warfarin. Daiichi believes the (b) (4) to be appropriate for achieving maximum efficacy while maintaining safety.

FDA recommended that Daiichi study two doses and further explore the dose response relationship. Daiichi noted that FDA characterized the dose/exposure-response as shallow, while they regard the 60 mg dose as appropriate. Daiichi commented that there was limited feasibility and potential viability in conducting a two-dose-study. Daiichi also expressed concern potentially exposing thousands of patients to a suboptimal dose. FDA reminded Daiichi of the risk of proceeding with only a 60 mg dose and noted that with a 30 mg dose safety may be preserved but if the incidence of bleeding is exceeded using the 60 mg dose they may need to redo the entire study. Daiichi stated that they were aware of the risk of proceeding with a 60 mg dose and noted that at the time of implementation (March, 2010), they will have a better safety profile of the drug and they will also rely on their Data Safety Monitoring Board (DSMB) to guide them. Daiichi acknowledged the FDA concern, however, both doses have been carefully considered internally, and Daiichi feels that its goal to achieve maximum efficacy while maintaining the safety profile is better achieved using only the 60 mg dose.

FDA stated that with warfarin the primary adverse reaction is bleeding. FDA inquired of Daiichi what the advantage of DU-176b would be compared to warfarin. Daiichi noted they do not know what the effect will be on the safety profile. They stated that the monitoring of international normalized ratios (INRs) is necessary for warfarin and the frequent monitoring is disliked by patients. Daiichi feels that patients might be more compliant with DU-176b than warfarin. The program hopes to see a slight decrease of bleeding in the range of a 10-20% reduction.

*FDA emphasized that the sponsor has proposed a single study and will need extra effort to manage the INRs in the warfarin arm and will have to ensure control. FDA advised that it will not be sufficient to provide merely the standard of care. Excellence in the management of the warfarin arm must be achieved. The adequacy of the warfarin control using the INR (i.e., quality and compliance with management of anticoagulation) will be an important review issue. FDA does not believe that it is adequate to perform INRs as infrequently as monthly during the trial, and advises that the frequency be increased. FDA does not believe (b) (4) (b) (4) is adequate for optimal warfarin dosing.

Daiichi acknowledged the FDA concern and agreed to provide assurance, particularly in other parts of the world, through vigorous education and implementation, to achieve an adequate level of INR control.

FDA stated that it does not object to the 60 mg dose selection. Although FDA is providing advice to company; it is the company's decision. The sponsor agreed to provide additional information regarding the rational for the decision to the Agency.

*FDA commented that the proposed dose reduction in subjects with a body weight less than or equal to 60 kg is primarily based upon a study in Japanese patients (Study J225) that showed subjects with a body weight of less than or equal to 60 kg had a higher incidence of bleeding than those with a body weight greater than 60 kg. It is unclear if this is a race effect or a true body weight effect. FDA requests that the sponsor address the issue of weight-based dosing in the proposed Phase 3 protocol.

*FDA noted that the sponsor proposed dose reduction in patients on strong P-gp inhibitors; however, the Phase 3 protocol states that these subjects would be excluded from the trial. FDA stated because Daiichi already proposes a dose reduction in these subjects, it is better to include

them in the trial, which would broaden the spectrum of recruitment as well as help capture some pharmacokinetics and pharmacodynamics (PK/PD) and efficacy/safety data.

Daiichi will consider examining the effect of race in exploration of the data. They do not expect race to be a factor. Daiichi will provide more information, regarding dose adjustments, to the application and include a technical report. Regarding the exclusion of patients on strong P-gp inhibitors, Daiichi stated it is unlikely to determine the correct dose adjustment. They acknowledge that it would limit their database and have implications for both the labeling and the statistical analysis; however, they prefer to perform a smaller study later in these populations.

*FDA expressed concern that the variability in the initiation of the study drug dose regimen, as it applies to the time of administration of heparin (between 5 and 12 days); FDA noted that variability in the study drug initiation time may have an effect on the frequency of recurrent VTE. This variability should be addressed. Consideration should be given for the administration of a dummy-drug in both arms of the trial during the heparin administration phase of treatment. FDA commented that, in effect, multiple dose regimens are being tested (based on variations in the time of initiation of the study drug with respect to discontinuation of heparin). This may present a challenge in analyses of the data as well as in labeling of the product.

Daiichi expects approximately 80% of patients to begin on Day 5 or 6 and a minority to start later. FDA inquired how Daiichi would write their labeling. Daiichi proposes to use the labeling language (b) (4) FDA cautioned that Daiichi would have to show data to support such a claim (i.e., that safety and efficacy are maintained at each of the potential times of study drug iniation). Daiichi acknowledged FDA concerns and stated it intends to provide a statistical and clinical basis for their proposal..

FDA commented that many aspects of the study are left to the discretion of the physician, including the choice of administration of either low-molecular-weight heparin or unfractionated heparin. FDA cautioned that this could lead to site differences. Many of the aspects of the study design may present challenges for the data interpretation. FDA inquired if the sponsor could study a fixed dose. Daiichi responded that it would be difficult and would lead to unblinding. Daiichi acknowledged FDA concerns and has discussed the options internally. They feel these concerns are trade offs associated with conducting a double-blinded study.

Slides 15-16 (Question 4)

Daiichi commented that a hazard ratio of 2.0 retains 50% of warfarin's effect. Daiichi proposed to rule out a hazard ratio of (b) (4) showing that DU-176b retains at least 70% of warfarin's effect. Daiichi noted this can only be achieved if the point estimate of the hazard ratio is at least as favorable as 1.17, corresponding to retaining 90% of warfarin's effect. Daiichi inquired if the non-inferiority margin of (b) (4) was acceptable.

FDA asked what the presumed benefit of treatment with edoxaban compared to warfarin was. Daiichi mentioned that patients might be more compliant and willing to undergo treatment without the inconveniences of warfarin. Daiichi acknowledged the utility of warfarin and stated if they could maintain efficacy with no loss of safety they will have advanced the field.

FDA emphasized that from a regulatory perspective, the non-inferiority margin of (b) (4) generally appears inappropriate. FDA cannot provide agreement with the proposal, given the available

data. FDA requested additional justification of the proposal or another analytical approach to ensure retention of efficacy (not importantly different from warfarin's efficacy).

Slides 17-20 (Question 2, 6, and 7)

The Sponsor proposed [redacted] (b) (4) FDA clarified that (b) (4) this request is a deviation from standard practice. FDA reminded the sponsor that since this question was not included in the original list of questions; the Agency would need more time to consider this issue and could not provide comments at this time. FDA suggested more thorough justification of the proposal.

Note:
* denotes additional FDA comments not originally sent to the sponsor.

DECISIONS (AGREEMENTS) REACHED:

- Daiichi must ensure sufficient anticoagulation (based on INRs) in the warfarin arm of the study.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- Determination of the acceptability of exempting myocardial infarction, stroke and cardiovascular death adverse events from expedited seven or 15 day reports for the Phase 3 studies.

ACTION ITEMS:

- Daiichi will provide more information, regarding dose adjustments, to the application including a technical report.

ATTACHMENTS/HANDOUTS:

- Sponsor Questions and FDA responses
- Daiichi Slides

Meeting Date: April 29, 2009

Time: 10:00 – 11:30 AM EST

Type: End of Phase 2 (Type B)

Product: DU-176b

Sponsor: DAIICHI SANKYO, INC.

Purpose: To obtain FDA feedback on the adequacy of their Phase 3 program to support the proposed indication: (b) (4) treatment (b) (4) (b) (4) of (b) (4) venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE)."

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **April 29, 2009** between **DAIICHI SANKYO, INC.** and the Division of Medical Imaging and Hematology Products. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Sponsor Questions and FDA Response:

QUESTION 1 (Target Population):

A. Does the Division agree with the proposed study population, including the adjudicated diagnostic criteria to be used by the CEC?

FDA Response:

The proposed study population and the adjudicated diagnostic criteria to be used by the CEC are acceptable. It might be beneficial to stratify patients as to whether the VTE is idiopathic or secondary to a thrombogenic event (tumor, recent surgery/trauma, immobilization, pregnancy/estrogen use, previous VTE, inherited/acquired thrombophilia).

B. Does the Division agree with the proposed inclusion and exclusion criteria for the Phase 3 study?

FDA Response:

The population for your phase 3 study should reflect the target population for whom the drug is intended and the protocol should provide for adequate monitoring of these patients for safety during the conduct of the study. Your extensive exclusion criteria may lead to restriction of the population in the product label and may necessitate conduct of additional studies in certain patients (e.g., hepatic impairment, renal impairment).

You should provide in the protocol more specific definition of "therapeutic dosages of anticoagulant treatment".

QUESTION 2 (Treatment Regimen): *Does the Division agree with the edoxaban treatment regimen (open-label heparin bridge, active and control arms) for the planned Phase 3 study?*

FDA Response:

It is unclear why 60 mg QD was chosen over 30 mg QD given 1) the relative small number of patients on each dose in study PRT011, 2) the unexpected finding that the incidence of bleeding did not appear to be correlated with DU-176b exposure in PRT011 contrary to PRT007 and previous AF studies, and 3) the shallow dose/exposure-response for the incidence of VTE. We recommend that you further explore the dose response relationship in a Phase 2 dose response study or explore both the 30 mg and 60 mg QD doses in your Phase 3 study in a manner similar to your atrial fibrillation phase 3 study.

The proposed dose adjustments by 50% for subjects with moderate renal impairment (CrCL $\geq$30 $\leq$50 mL/min), body weight $\leq$ 60 kg, or concurrently receiving a strong P-gp inhibitor is acceptable.

Additional Clinical Pharmacology Comment:

Considerable variability in the DU-176b exposure is observed following a fixed dose of DU-176b (e.g. 10-fold difference in minimum and maximal trough concentration follow 30 mg (3-35 ng/mL) and 60 mg (5-65 ng/mL) QD). When exposure is highly variable and there is a dependence of response (VTE or bleeding) on exposure, it could be important to e.g. individualize each patient's dose, restrict concomitant medication, or administer the drug under fasting conditions in order to attain the full potential for efficacy and reduce the risk of bleeding. Please describe your considerations on concomitant aspirin use and whether DU-176b should be taken with our without food in the phase III study (Concomittant administration of aspirin was found to increase the relative bioavailability by 33% and food was shown to reduce the absorption rate by 64% in the population PK analysis).

The adequacy of warfarin control using the international normalized ratio (INR) (i.e., quality and compliance with management of anticoagulation) will be an important review issue. Every effort should be made to ensure excellence in management of INR. Also, evaluation of any possible interaction between treatment effect and the various allowed initial short course anticoagulation treatments will be a review issue

QUESTION 3 (Study Design/Objectives): *Does the Division agree that the proposed endpoints of the pivotal Phase 3 study are adequate to support the proposed indication: "for* (b) (4) *treatment* (b) (4) *of* (b) (4) *venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE)"?*

A. Does the Division agree that the proposed primary endpoint at 12 months and the secondary endpoints of the pivotal Phase 3 study are appropriate?

FDA Response:

The proposed primary endpoint at 12 months (symptomatic recurrent VTE to include a composite of DVT, non-fatal and fatal PE) as documented by the CIAC is acceptable. Additional secondary outcomes should include separate analyses of the components of the primary endpoint.

The outcomes in the Per Protocol and the ITT Population should be similar in direction and degree.

The definitions of the endpoints are acceptable except:

- **You should provide data that supports your descriptions of symptomatic DVT in patients with "previous DVT investigations".**
- **The definition of fatal PE as a "death which cannot be attributed to a documented cause and for which PE/DVT can not be ruled out" will require certainty as to absence of documentation of other etiologies, particularly for cardiac causes.**

Evaluation of death due to any cause will be an important review issue for safety.

B. Does the Division agree that the proposed definitions for "major bleeding", "clinically relevant bleeding", and "minor bleeding" events are appropriate?

FDA Response:

The definition of "major bleeding" is acceptable. The proposed definitions for "clinically relevant bleeding" and "nuisance bleeding" are likely to overlap because the criteria for many of the "clinically meaningful bleeding" events are subjective.
Among the analyses include some evaluation of all bleeding as well.

C. Does the Division agree that the expected subject treatment durations (i.e., 10% for only 3 months, 40% for only 6 months, and 50% for 12 months) support the proposed indication: "for (b) (4) *treatment* (b) (4) *of* (b) (4) *venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE)"?*

FDA Response:

The distribution of duration of maintenance anticoagulant therapy is acceptable to support the indication, so long as that is the distribution that actually emerges during the trial. Consider that if these proportions may not apply to patients enrolled in the trial, there could be an important interaction of treatment duration with regard to outcome. If duration of treatment is to be left to the physician after 3 months treatment, effect of treatment duration may be confounded with site/investigator, also.

All patients should be followed for the primary outcome for the same length of time so that, at the conclusion of the trial, data will be available that would provide the optimal duration of therapy for the indication.

Evaluation and interpretation of the study results may be complex and will be a review issue,

QUESTION 4 (Statistical Methods):

A. Does the Division concur that the planned statistical analyses and the rationale relating to sample size, non-inferiority margin (b) (4) *for hazard ratio), and test of significance level (α=0.05 for non-inferiority, α=0.01 for superiority) in the study support the proposed indication?*

FDA Response:

No. The hazard ratio of (b) (4) **may retain only 70% of warfarin's effect compared to placebo. A greater percentage (85-90%) retention of warfarin effect is desirable.**

B. The planned statistical analysis as specified in Figure 2.1, specifies that if non-inferiority is demonstrated for the edoxaban treatment regimen, then testing of superiority to warfarin will be performed at a nominal significance level of α=0.01. Does the Division agree that this statistical procedure is appropriate to demonstrate superiority?

FDA Response:

This appears to be acceptable. Superiority testing should include all-cause, rather than VTE-related, mortality.

C. The primary analysis of the primary efficacy endpoint will be based on the modified Intent-to-Treat (mITT) Analysis Set (including all randomized subjects who receive at least one dose of study drug). This analysis will include all events that occur during the 12 months study period, including events that occur while off study drug. Does the Division concur with this mITT analysis method as the primary analysis for the primary efficacy endpoint?

FDA Response:

There should be approximately equal numbers of patients whose anticoagulant therapy ends at each time interval, so that the duration of each therapy is the same in both arms of the trial. If there is an imbalance in the length of therapy, interpretation of the results would be difficult.

Please note: the censoring distribution for the two arms should be equal while using the Cox model. Based on the Agency's prior review experience, it is suggested that age should be an important covariate and should be included in the Cox model.

D. The analysis of efficacy endpoints as planned in Figure 2.1 will employ the proportional hazards model with treatment and stratification factors as covariates. Does the Agency concur?

FDA Response:

This appears to be acceptable.

The Cox proportional hazard model for the primary efficacy endpoint and graphical methods for the assumption of proportional hazards appears to be acceptable. Please specify the alternative method for the analysis of the primary efficacy endpoint if the assumption is violated.

E. The primary analysis of primary efficacy endpoints will be based on symptomatic VTE for the mITT analysis set as noted in question 5C above. Summary statistics and 95% CIs will be generated (a) for patients who at baseline had DVT without PE and (b) for patients who at baseline had PE, but no formal statistical hypothesis test will be performed within each group. Does the Division concur that the analysis on the mITT analysis set is primary and the by-group analysis should be only supportive?

FDA Response:

This appears to be acceptable.

QUESTION 5 (Clinical Program): *Does the Division concur that this single Phase 3 study, taken together with the Phase 2 VTE prophylaxis studies (PRT007, PRT 011) and provided that its results are sufficiently compelling, adequately supports the proposed indication?*

FDA Response:

This may be acceptable but results are a review issue. Generally, two adequate and well-controlled studies are needed for a new indication. The adequacy of a single study to support approval of a new indication will be determined by its ability to support the efficacy claim based on strength of the results. Internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results will be considered in the evaluation. See "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May, 1998"

Also, note that non-inferiority studies are less likely to be persuasive.
Thus, there is a risk in performing a single study that may not have convincingly positive results.

The Phase 2 studies PRT007 and PRT011 (VTE prophylaxis in hip replacement surgery patients) are likely to have limited applicability to the indication being sought.

QUESTION 6 (Safety Population and Exposure): *Does the Division agree that the safety data expected to be available at the time of NDA submission will adequately support the review, registration, and approval of edoxaban for the proposed indication?*

FDA Response:

The adequacy of the safety data to support an NDA application is a review issue. It would be preferable to submit all safety data from the ongoing trial of edoxaban in atrial fibrillation (ENGAGE AF-TIMI 48). A safety database which includes several thousand patients exposed to edoxaban in completed, fully reported controlled clinical trials in your NDA submission is desirable. Based on your projections, there should be approximately 375 persons exposed to edoxaban for 3 months, 1500 persons for 6 months and 1875 persons for 12 months. Please explain the differences in the expected number of exposed persons.

QUESTION 7 (Serious Adverse Event Reporting): Does the Division agree to the process of serious adverse event (SAE) reporting proposed for the study as outlined and the reporting of serious unexpected adverse reactions to the Agency in a blinded manner (i.e., study drug will remain blinded)?

FDA Response:

This appears to be acceptable.

QUESTION 8 (Clinical Pharmacology): Does the Division concur that the proposed clinical pharmacology program is adequate for the initiation of the planned Phase 3 study in VTE and also for the NDA filing?

FDA Response:

Yes, provided the studies outlined in Table 3.1 of your meeting package are completed and submitted including datasets (SAS transfer files). In addition, we recommend that the sponsor evaluate the effect of renal impairment combined with moderate CYP3A/P-gp inhibition on edoxaban exposure. For example, would mild renal impairment combined with a moderate CYP3A/P-gp result in a clinically relevant increase in exposure?

QUESTION 9 (Pediatric Development): Does the Division agree to DSPD's request for a deferral of pediatric studies until after the safety and efficacy of edoxaban has been established for adults?

FDA Response:

A request for deferral of pediatric studies should be submitted with the NDA for determination by the Pediatric Review Committee.

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Linked Applications	Sponsor Name	Drug Name / Subject
IND 63266	DAIICHI SANKYO INC	DU-176B

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/s/

MARCUS A CATO
05/28/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,266
IND 77,254

Daiichi Sankyo, Inc.
Attention: Paulette F. Kosmoski
Executive Director, US/EU and Regional Regulatory Affairs-CMC
399 Thornall Street
Edison, NJ 08837

Dear Ms. Kosmoski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DU 176b.

We also refer to the meeting between representatives of your firm and the FDA on November 6, 2008. The purpose of the meeting was to discuss the CMC development strategy needed to support the registration of DU-176b tablets.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Safety Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 6, 2008
TIME:	1:00 – 2:30 PM
LOCATION:	White Oak Campus, Building 22, Room 1311
APPLICATION:	IND 63,266 and IND 77,254
DRUG NAME:	DU 176b
TYPE OF MEETING:	End of Phase 2 (CMC)

MEETING CHAIR: Sarah Pope, Ph.D.

MEETING RECORDER: Diane Leaman

FDA ATTENDEES: (Title and Office/Division)

Division of Medical Imaging and Hematology Products

Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Diane Leaman, Safety Project Manager
Marcus Cato, Regulatory Project Manager

Office of New Drug Quality Assurance

Sarah Pope, Ph.D., Acting Branch Chief
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead
Kasturi Srinivasachar, Ph.D., Pharmaceutical Assessment Lead
Lyudmila Soldatova, Ph.D., Chemist
Christine Moore, Ph.D., Acting Deputy Director
Ravindra K Kasliwal, Ph.D., Chemist
Deborah Mesmer, Project Manager, Quality
Scott Goldie, Project Manager, Quality
Joyce Crich, Ph.D., Chemist

EXTERNAL CONSTITUENT ATTENDEES:

Daiichi Sankyo, Inc.

Tetsuya Araki, Ph.D., Manager, Analytical & Quality Evaluation Research Laboratories
Koutaro Kawanami, Associate Senior Researcher, Process Technology Research Laboratories
Motonori Kidokoro, Ph.D., Senior Researcher, Formulation Technology Research Laboratories
Paulette Kosmoski, Executive Director, US/EU & Regional Regulatory Affairs-Chemistry, Manufacturing and Control (CMC)
Hiroyuki Nakata, Associate Senior Researcher, Analytical & Quality Evaluation Research Laboratories

Linda Nelson, Ph.D., Associate Director, Regulatory Affairs-CMC
Fraser Pickersgill, Ph.D., Director, CMC Management & Operations
Sadahiro Shimizu, Manager, CM&C Planning Department

BACKGROUND:

On August 11, 2008, Daiichi Sankyo, Inc. (Daiichi) requested a combined End-of-Phase 2, CMC meeting with the Division of Medical Imaging and Hematology Products (DMIHP) and the Division of Cardiovascular and Renal Products (DCRP) CMC reviewers. On October 1, 2008, Daiichi submitted a background package for the meeting. On October 31, 2008, DMIHP sent via telefacsimile preliminary FDA responses to the sponsor's questions from the October 1, 2008 background package (see attached). On October 5, 2008 (revised October 6, 2008), Daiichi provided overhead slides for the November 6, 2008 meeting (see attached).

MEETING OBJECTIVES:

To discuss the CMC development strategy needed to support the registration of DU-176b tablets

DISCUSSION POINTS:

Daiichi Sankyo agrees with the FDA responses to Questions 2, 6 and 7. The sponsor requests clarifications on Questions 1, 3, 4, 5, 8 and 9.

Question 1.
Does the FDA agree with the proposed designation of (b) (4) *as the starting materials and their related controls used in the commercial manufacturing route of DU-176b drug substance?*

Discussion
The sponsor confirmed that the (b) (4) reference standard is obtained from high-purity lots of material. The Agency acknowledges the strategy for this reference standard is acceptable.

Because (b) (4) is hazardous (b) (4) the sponsor said that they do not currently have in-house testing for (b) (4). The sponsor performs a visual identification of the (b) (4) label and records lot numbers upon receipt. The sponsor confirmed that (b) (4) hydrolyzes quickly and releases (b) (4) which is hazardous to personnel and also compromises the material. The Agency noted that (b) (4) The Agency recommends that the sponsor develop appropriate in-process controls and provide a full justification (including a manufacturer CoA) in the NDA.

The sponsor requested Agency agreement with the designation of (b) (4) as a regulatory starting material and the proposed control strategy for (b) (4). The Agency responded that the strategy is reasonable and that a final determination will be made during the NDA review.

The sponsor confirmed that a high-purity lot for the [(b) (4)] reference standard has been established. The sponsor will provide data in the NDA regarding the [(b) (4)] reference standard, [(b) (4)] evels, proximity to the drug product and additional pertinent information.

The Agency also reminds the sponsor to submit unspecified impurity and individual impurity profiles for [(b) (4)] in the NDA.

Question 3.

Does the FDA agree that residual [(b) (4)] is suitably controlled in the [(b) (4)] starting material and that an individual test is not warranted in the final drug substance specifications?

Discussion
The sponsor plans to use atomic absorption for [(b) (4)] The Agency notes that the approach appears to be acceptable and that the sponsor should provide the data in the NDA. The Agency confirmed that the overall determination of the data is a review issue. The sponsor agrees to provide corresponding information regarding the proposed assessment in the NDA.

Question 4.
Does the FDA agree that the potential for the formation of [(b) (4)] in the drug substance manufacturing process is unlikely to occur and that an individual test is not warranted in the final drug substance specifications?

The Agency commented that this approach could be acceptable if the levels of [(b) (4)] are in line with the levels in the commercial batches and if additional manufacturing information is provided to support continued low levels. The Agency recommends that the sponsor consider submitting data demonstrating how the impurities are formed and removed in the process (e.g., amount produced under various reaction conditions, amount removed in the [(b) (4)] [(b) (4)] The Agency also asked the sponsor to describe what "significant process changes" would initiate testing for revalidation purposes. The Agency recommends that the sponsor accompany the proposal with a complete justification, including data from a suitable number of commercial batches (e.g., ten batches of historical data). The Agency confirmed that the sponsor's proposal to include batch data [(b) (4)] may not be adequate to support this proposal, and that additional batch data may be needed.

The Agency notes that sunset provisions for periodic testing could be justified. The sponsor said they might have data at the time of NDA submission. The Agency confirmed that, should the sponsor request guidance on this issue, it can be revisited at their pre-NDA meeting.

Question 5
Does the FDA agree with the testing regimen for final release and stability for drug substance?

Discussion

Question 7
Does the FDA agree with the testing regimen proposed for the drug product listed for release and stability purposes?

The Agency agrees with the proposed approach. The final determination of acceptability will be made during the NDA review.

Question 8.
Does the FDA concur with the overall proposed strategy for the application of Quality by Design (QbD) and (b) (4) *for the manufacture and control of DU - 176b drug product?*

The Agency notes that, while not enough information is presented for evaluation, the Quality by Design (QbD) approach presented appears to be systematic and risk-based. The sponsor wanted clarification on whether the path they proposed is acceptable? The Agency responded that it is a reasonable approach.

Question 9
Does the FDA agree with the proposed reduced stability designs for the registration drug product stability program to support the primary stability data package for the NDA submission?

The sponsor notes that they may have additional information regarding this topic by the time of the Pre-NDA meeting.

Additional comments:

The Agency asked the sponsor if they planned to retain the seven-count bottle and whether it was a commercial bottle or physician sample. The sponsor responded that they wanted to retain the seven-count bottle as a physician sample. [redacted] The Agency asked if the sponsor was planning to continue to include it in the post-approval stability design. The sponsor replied that they plan to keep it in registration. The sponsor will include data on post-approval batches in annual reports. They will not discontinue the physician samples post-approval. The Agency notes that the Division of Medical Errors and Prevention (DMEP) may comment on the labeling during the NDA review (or prior, as applicable).

The Agency asked the sponsor how content uniformity is confirmed. The sponsor clarified that they currently take [redacted] The sponsor intends to [redacted] For the drug product specifications, the Agency recommends that the sponsor consider how the larger sample size [redacted] could be used with statistically relevant acceptance criteria. Furthermore, the Agency advises the sponsor to consider how models, such as a [redacted] would be maintained under their proposed quality system.

The sponsor thanked the Agency for the ongoing dialogue regarding this product. The Agency notes that a good time to discuss additional QbD aspects would be at the pre-NDA meeting.

The Agency confirmed that the sponsor should continue to submit related IND comments to both INDs. Future meeting requests and desk copies can also be sent to both INDs. For a combined meeting, please designate a lead IND. The sponsor can also submit proposals and questions to INDs, as applicable.

DECISIONS (AGREEMENTS) REACHED:

The sponsor will provide information in the NDA as outlined in the meeting discussion. The sponsor will present additional discussion items, or extensions of these discussion items, in a pre-NDA meeting request at a later date.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None.

ACTION ITEMS:

The Agency will send meeting minutes to the sponsor within 30 days.

ATTACHMENTS/HANDOUTS:

Attachment A: FDA telefaxsimile of preliminary responses to sponsor questions

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Linked Applications	Sponsor Name	Drug Name
IND 63266	DAIICHI SANKYO INC	DU-176B
IND 77254	DAIICHI SANKYO	DU 176B

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/s/

DIANE V LEAMAN
11/25/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 77,254

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DU-176b.

We also refer to your amendment dated October 7, 2008, containing a request for clarification to the FDA's End of Phase 2 Meeting Minutes dated September 24, 2008.

We have the following responses to your points of clarification:

1. Regarding the target population for your Phase 3 study, an approximate target of 60% vitamin K antagonist (VKA)-experienced subjects rather than a strict cap at 60% is acceptable.
2. Please disregard the Additional Discussion During Meeting section topic concerning the primary efficacy analysis (Question 7). The response regarding this topic in the clinical special protocol assessment (SPA) dated October 15, 2008 supersedes this discussion.
3. The Division agrees with your plans of a modified intent-to-treat (mITT) analysis. Please see the Division's October 15th response to your plans detailed in the SPA.
4. We agree with your list of events expected in this patient population and agree that they should not be submitted to the Division in an expedited manner with one exception. Non-CV deaths should still be reported in a 15-day safety report.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 77254	DAIICHI SANKYO	DU 176B

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/s/

NORMAN L STOCKBRIDGE
10/17/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 77,254

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Investigational New Drug Application (iND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DU-176b.

We also refer to your September 11, 2008, submission requesting a special clinical protocol assessment, received September 12, 2008. This protocol is 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".

We have completed our review, and based on the information submitted, have the following responses to your questions. These responses formally document our agreements concerning the above referenced protocol:

1. Based upon our discussion at the End of Phase 2 meeting on August 13th, the protocol inclusion criteria section, Section 4.1.1 has been clarified. Therefore, patients with either paroxysmal or persistent/permanent AF will be included and monitored. Also warfarin-naïve and warfarin-experienced patients will be included. It is expected that the warfarin-naïve patients will comprise less than or approximately 40% of the total enrollment, and will be monitored.

   Additionally, as agreed upon at this meeting, stratification based upon warfarin (experienced vs. naïve) was not considered necessary due the size of the study and overall stratification scheme based on CHADS2 score, creatinine clearance and concomitant medications.

   Does the Agency concur with these changes made to the protocol?

   Response:
   All of these changes are acceptable. However, the use of the CHADS2 score for eligibility could result in studying a population that is substantially different than those of the historical trials used to calculate the non-inferiority margin. If the population studied is sufficiently different and the constancy assumption is violated, then the non-inferiority analysis may not be valid. Please collect the details of the CHADS2 score determinations and the risk factors used for eligibility

determinations in the historical trials as well as type of AF and prior warfarin use so that we can understand how the population to be studied will compare to the historical trial populations.

2. Does the Division concur that the planned statistical analyses and the rationale relating to sample size, non-inferiority margin (1.38 for risk ratio), and test of significance level (α=0.05 study-wise), in study DU176b-C-U301, support the proposed indication?

   Response:
   The Agency recommended in the August 13th meeting that superiority testing is entertained only for the high dose regimen with a p-value of 0.01 or smaller. If you still plan to test superiority for the three dose regimens, we recommend a total type I error rate of 0.01 or less, instead of the 0.05 level. This also applies to testing superiority on the secondary endpoints.

3. In order to control the study-wise type I error rate of 0.05, the statistical analysis plan (SAP) will use a splitting alpha test procedure as detailed in Section 11.4.1 of the protocol. Does the Division concur?

   Response:
   Yes, the Division concurs. Also, see the response to Question 2 regarding the alpha level for testing superiority.

4. If either DU-176b treatment group or part of a treatment group is terminated before the study ends due exclusively to safety concerns (life threatening bleeding, intracranial hemorrhage or all cause mortality), then the analysis will treat the study (b) (4) (b) (4) For examples, see protocol Section 11.4.1, Tables 11.4 and 11.5.

   Response:
   No, we do not agree. If any DU-176b regimen is terminated, the remaining regimens should be tested at the alpha/3 significance level since the safety endpoint overlaps considerably with the primary efficacy endpoint and hence selection bias in terms of type I error inflation needs to be carefully considered. Also, see the response to Question 2 regarding the alpha level for testing superiority.

5. If the DU-176b 30 mg qd Allocated regimen (30 mg subjects in the High Exposure group and 30 mg subjects in the Low Exposure group) is non-inferior to warfarin with regards to efficacy and has a safety profile comparable to or better than warfarin, does the Division agree that the DU-176b 30 mg qd regimen may be recommended for use in the product labeling?

   Response:
   Whether the 30-mg qd regimen may be recommended is a review issue based on all trial results. If renal function and metabolic inhibitor-based dosing produces superior results, then the adjusted dosing may be recommended regardless of whether the 30-mg qd regimen produces non-inferior results to warfarin.

6. The planned statistical analysis specifies that (b) (4) (b) (4) Division agree that this statistical procedure is appropriate to demonstrate superiority?

Response:
No, we do not agree. Please see our response to Question 2.

7. The primary analysis of the primary efficacy variable will be based on the mITT Analysis Set, which adopts an on-treatment analysis approach. The on-treatment analysis includes events that occur on days subjects have received study drug plus 3 days post-dose (based on approximately five half-lives of DU-176b). Events that occur on days that a subject missed a dose will still count. Events that occur during a planned study drug interruption will not count unless it occurs within 3 days post-dose. Does the Division concur with this mITT analysis (on-treatment approach)? Does the Division agree with the mITT analysis as primary?

   Response:
   Your proposal only to count events within 3 days post-dose seems reasonable clinically. However, precise date determinations in trials have been problematic so you will need to be particularly careful in collecting dates of final study drug use as well as of the events, collect all events regardless of whether the event is within the 3 day window, and have your endpoints committee verify the dates blinded to treatment. Furthermore, we will perform a sensitivity analysis based on all events. If the analysis based on all events is substantially different than that based on 3 days post-dose, then interpretation will be difficult.

8. The primary analysis (on mITT analysis set) of primary efficacy variable (time to first occurrence of Stroke/SEE) will employ the proportional hazards model to establish non-inferiority. The testing for superiority will be performed using a log-rank test based on the ITT analysis set. Does the Agency concur?

   Response:
   We agree.

9. At the study and site initiation training, the importance of maintaining an INR range (2-3), as per AHA/ACC/ESC guidelines, will be emphasized. The point of care device is used to measure the INR values. The investigator will see only the encrypted code but not the actual INR value. The investigators will provide the code to the IVRS center. The actual INR values for warfarin subjects and the sham INR for the DU-176b subjects will be provided by the IVRS to the investigators. The INR ranges will be monitored during the study. The investigators and site monitors will be provided timely feedback on subjects within the desired range (INR range within 2-3) and outside of the desired INR range. Thus, DSPD will ensure that the warfarin group is well managed to have INR in the target range (Time in Therapeutic Range/TTR) for the majority of patients.

   Does the Division concur with this approach?

   Response:
   Please collect data on time in therapeutic range for both groups (sham INR for the DU-176b subjects) and INRs for the DU-176b as well as the warfarin. We also recommend that you monitor whether investigators appear to be making appropriate modifications to dosing based on reported INR, so that you can institute coaching where needed.

In addition, we have the following comments.

Clinical Pharmacology

1. The individual contributions to the observed increase in the exposure to DU-176 through inhibition of P-gp and CYP 3A are not known for many of the strong and moderate CYP3A/P-gp inhibitors. Therefore, the selection of prohibited and non-prohibited CYP3A/Pgp inhibitors appears somewhat arbitrary. Ritonavir is prohibited, whereas nelfinavir, indinavir and saquinar are not. Ketoconazole, itraconazole, erythromycin and clarithromycin are prohibited (except for short term use), but co-administration of nefazodone is permitted. Please provide a rationale.

2. The dose of DU-176b is halved for subjects on quinidine and verapamil. However, Cmin,ss of DU-176, the best predictor for bleeding is only increased by a factor of 1.2 to 1.3 in the presence of these drugs. Please provide a rationale.

3. The exclusion criteria on p.19 include "subjects receiving prohibited concomitant medications..... potent P-gp inhibitors.....". However, from p. 126 it is appears that short term use of these drugs (<10 days) is permissible. Please clarify.

   Also, in order to avoid confusion use "CYP3A/P-gp inhibitors" instead of "P-gp-inhibitors".

4. The active metabolite DR21-2393 is measured, but the section on data analysis does not indicate what will be done with the metabolite data. Please clarify.

5. The List of PK-PD objectives in "Study Objectives and Hypotheses" (p.40) proposes many more evaluations than those stated in "PK/PD Analyses" (p.95). Please clarify.

6. Blood samples for the determination of the D-dimer will be collected at baseline, and on the Day 29 and 3 Month Visits. The protocol does not state how many blood samples will be collected or whether the collections occur simultaneously with those for the population PK. Please clarify.

7. A baseline PK sample prior to initiation of the treatments should be collected.

8. The protocol should indicate how the recording of date/time of the last dose before the PK sample and the date/time of the PK sample collection will be secured.

Clinical

1. Your proposed doses and daily dosing regimen are based on your analyses of the prior studies. We find it remarkable that the threshold of 1.2 x typical C_{min} was the most robust predictor of bleeding in PRT018. We would like to receive the data sets for PRT018 to confirm your results and a more detailed justification of your proposed doses and dosing regimen.

2. Please define in your protocol trigger conditions (page 30 of 34 of the draft CEC charter) and document how they will be detected and handled. Please document separately investigator-reported events, events that are modified, added, or deleted by any data clarification process, and triggered events. Please differentiate in any data sets submitted these three event variations.

3. Please define in your protocol how CrCL will be calculated.

4. Provide an encrypted copy of the randomization list for the study prior to study enrollment. Provide the encryption key in the NDA study submission.

5. Provide a sample of the clinical supplies, including masked study drugs and labeling, for each arm of the study.

6. Provide a copy of your finalized statistical analysis plan, including details of handling trigger conditions and missing data, prior to enrollment of substantial numbers of patients.

7. Provide in a data set for each case the results of the adjudications by reviewer in your NDA study submission. Provide the signed and dated adjudication forms as case report forms (CRFs) for the required CRF submissions (deaths and withdrawals).

8. Provide the results of your quality control on the adjudications in your NDA study submission.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 77254	DAIICHI SANKYO	DU 176B

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

/s/

NORMAN L STOCKBRIDGE
10/15/2008

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted via email:	dmorgan@dsus.com
Attention:	Doreen Morgan
Company Name:	Daiichi-Sankyo
Phone:	(973) 590-5198
Subject:	**IND 77,254 13Aug08 End of Phase 2 Meeting Minutes**
Date:	24 September 2008
Pages including this sheet:	18
From:	**Alison Blaus**
Phone:	**301-796-1138**
Fax:	**301-796-9838**

*********PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date:	13 August 2008
Application:	IND 77,254
Drug:	DU-176b Tablets
Sponsor:	Daiichi-Sankyo
Meeting Purpose:	End of Phase 2
Meeting Type:	Type B

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products
Ellis Unger, M.D.	Deputy Director
Robert O'Neill, Ph.D.	Director, Office of Biostatistics
James Hung, Ph.D.	Director, Division of Biometrics I
John Lawrence, Ph.D.	Mathematical Statistician
Valeria Freidlin, Ph.D.	Statistician
Jialu Zhang, Ph.D.	Statistician
Ram Tiwari, Ph.D.	Statistician
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Stephen Grant, M.D.	Medical Officer
Patricia Harlow, Ph.D.	Pharmacologist
Peter Hinderling, M.D.	Clinical Pharmacology
Christoffer Tornoe, PhD	Pharmacometrics
Edward Fromm	Chief, Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager
Russell Fortney	Regulatory Health Project Manager
Lori Wachter	Regulatory Health Project Manager

Daiichi Sankyo Pharma Development (DSPD):

Tomás Bocanegra, M.D.	Sr. Vice President, Clinical Development
Youngshook Choi, M.D.	Senior Director, Risk Management
James Hanyok, Pharm.D.	Senior Director, Clinical Development
Howard Hoffman, M.D.	Vice President, US/EU Regulatory Affairs
Satoshi Kunitada, Ph.D.	Vice President, Project Leadership
Jeanne Mendell-Haray, Ph.D.	Director, Clinical Pharmacology
James Molt, Ph.D.	Sr. VP Global Regulatory Affairs & Risk Management
Doreen V. Morgan, Pharm.D., M.S.	Executive Director, Regulatory Affairs
Indravaden Patel, M.D.	Executive Director, Clinical Development
Francis Plat, M.D.	Vice President, Clinical Development Cardiovascular
Daniel Salazar, Ph.D.	VP, Translational Medicine & Clinical Pharmacology
Minggao Shi, Ph.D.	Senior Director, Biostatistics
Donna Taneja, Ph.D.	Senior Director, Global Project Management
Daiichi Sankyo Co., Ltd.	
Masayuki Sato, Ph.D.	Associate Manager, New Drug Regulatory Affairs
Yoshimasa Shimoto, Ph.D.	Director, Global Project Management
Consultants:	
Eugene Braunwald, M.D.	Study Chairman

Elliott Antman, M.D.	Principal Investigator
Robert Giugliano, M.D.	Co-Principal Investigator

Background:

DU-176b is an inhibitor of coagulation factor Xa. The compound is administered orally as a tablet and is made available in two dosage strengths, 15 and 30 mg. DU-176b is being developed to reduce the risk of stroke and systemic embolic events (SEEs) in patients with atrial fibrillation (AF). There will be one pivotal trial in Phase 3 of development. This study, DU176b-C-U301, is a randomized, double-blind, parallel-group, event-driven, non-inferiority study with three treatment groups. The three treatment groups are a warfarin arm, a high dose DU-176b arm and a low dose DU-176b arm. In this end-of-Phase 2 meeting, Daiichi-Sankyo is aiming to reach concurrence on the proposed doses of DU-176b, the key statistical elements (primary and secondary endpoints, NI margin, etc.) and the adequacy of the sponsor's anticipated overall safety database at the time of NDA submission.

Prior to the meeting discussion, the sponsor presented slides on the planned design of the Phase 3 protocol, TIMI-48, and its corresponding statistical analysis plan. During the presentation of the slides, Dr. Temple suggested that it might be beneficial to consider creatinine clearance when stratifying the patients into either the low or high dose of each treatment arm. Dr. O'Neill added that the analysis plan was very similar to that of a PK modified dose-response curve.

Questions for the Division:

1. Does the Division agree with the DU-176b dosage regimens selected for the planned Phase 3 study DU176b-C-U301?

   Preliminary Response:
   Yes.

   Additional Discussion During Meeting:
   Dr. Grant stated he did not understand why the protocol did not allow dose adjustment for subjects who develop renal failure. The sponsor stated that the protocol had already been altered so that the dose will be adjusted. The Division asked the degree of factor Xa inhibition at C_{min}. Daiichi-Sankyo said that for the 60-mg dose it was close to 70%. The sponsor agreed to provide additional details in follow-up to this meeting.

2. Does the Division agree that the proposed primary endpoint of this single pivotal Phase 3 study is adequate to support the proposed indication: "To reduce the risk of stroke and systemic embolic events (SEEs) in patients with atrial fibrillation (AF)"?
   The proposed primary endpoint is a composite of stroke and SEE. Stroke includes any stroke (including hemorrhagic stroke, extradural hematoma, and intracranial hemorrhage but excluding transient ischemic attack [TIA]). Subdural hematomas will be included as intracranial hemorrhages but will not be classified as hemorrhagic strokes. SEE includes non-central nervous system (non-CNS) systemic embolic events. Precise definitions for these endpoints will be included in the clinical events committee (CEC) charter.

   Preliminary Response:
   Yes, we agree that the target indication is potentially supportable with the proposed study, because the historical trials used to estimate the treatment effect of warfarin had a composite of stroke and SEE as their primary endpoints.

Additional Discussion During Meeting:
No further discussion.

3. Target Population
   A. Does the Division agree with the proposed inclusion and exclusion criteria for the Phase 3 study? In particular, does the Division agree with the definition of AF as outlined in the inclusion criteria?

Preliminary Response:
More discussion is needed regarding the specifics of the intended subject population:
1. Inclusion of any subject with paroxysmal AF regardless of duration number of paroxysms.
2. Inclusion of subjects with sustained (chronic) AF.
3. Inclusion of both warfarin-experienced and warfarin-naïve subjects.
4. Whether the eligibility criteria will result in enrollment of a population similar to that enrolled in the historical studies used to estimate treatment effect of warfarin.

Additional Discussion During Meeting:
The division explained that the concern was that event rates in the trial might be lower than expected if patients with a single episode of atrial fibrillation within one year are included. Dr. Braunwald stated that event rates in the ACTIVE-W trial were similar in subjects with paroxysmal and sustained AF. The division pointed out that in ACTIVE-W patients had to have two episodes of AF two weeks apart within six months to be eligible to enroll. Dr. Temple suggested adding an interim analysis to look at event rates. Dr. Braunwald noted that regardless of paroxysmal vs. chronic AF, in a clinical setting the treatment would be the same. He quoted the EuroHeart study in which the outcomes for patients with permanent, paroxysmal and persistent AF were identical after one year treatment with Coumadin. He added that more inclusion criteria will be added to the final protocol by pre-defining the type of AF prior to randomization.

The sponsor agreed that both warfarin-experienced and warfarin-naïve subjects would be included in the study, but there will be a 60% cap on warfarin-experienced patients. Lastly, the sponsor acknowledged that differences between the population actually enrolled in their trial and the populations enrolled in the historical studies upon which the NI margin is based would complicate interpretation of their trial. In order to document this difference, the sponsor plans to examine differences in baseline characteristics such as age, concomitant medications, etc. between the upcoming Phase 3 study and past studies.

   B. The inclusion criteria require subjects to have documented history of AF (within the past 12 months) with $CHADS_2$ risk score ≥ 2 before randomization. The $CHADS_2$ score is based on two points for past history of stroke and one point for each of the other risk factors: diabetes, hypertension, heart failure, and age ≥ 75. Does the Division agree that the documented history of AF within the past 12 months is sufficient, regardless of the ECG rhythm observed during the 30 days before entry into the study? The rationale for allowing subjects in normal sinus rhythm at study entry but with past history of documented AF is to allow those with paroxysmal AF into the study.

Preliminary Response:
See answer to part A.

Additional Discussion During Meeting:
No further discussion.

4. Based on recent trends in enrollment of subjects in cardiovascular (CV) mega-studies, we may have a large number of subjects enrolled outside of the United States of America (USA). The USA study sites are anticipated to contribute approximately 10% of the total study population. Regardless of how many North American subjects are enrolled in this single pivotal study, does the Agency concur that this NDA registrational study will support an approval? If not, what is the minimum number of North American subjects the Division would consider acceptable?

Preliminary Response:
We have accepted registrational studies performed entirely outside of the U.S. We require that all sites allow auditing by our compliance group. Will all sites be using the same comparator agent?

Additional Discussion During Meeting:
The sponsor confirmed that all sites in the upcoming Phase 3 trial will be using the same comparator, Coumadin (warfarin). The division emphasized the need for the sponsor to monitor appropriately all sites regardless of location.

5. Does the Division concur that the planned statistical analyses and the rationale relating to sample size, non-inferiority margin, and test of significance (one-sided (b) (4) in study DU176b-C-U301 support the proposed indication?

Preliminary Response:
You will need to provide literature and all details to justify the relevance of NI margin of (b) (4). Validity of the constancy assumption needs to be explored, e.g., whether the population in the NI trial similar to those in the 6 historic studies. For the NI margin calculation, per the Agency's experience for this indication:

a) The July 2005 Duke Expert Meeting agreed on the NI margin of 1.38.
b) Table 4 in John Lawrence's review of NDA 21-686 shows the NI margin of 1.38.
c) The NI margin recommended by the Agency is 1.38.

The alpha level ought to be part of the same discussion.

Additional Discussion During Meeting:
Dr Temple reiterated that 1.38 was the recommended NI margin. Dr Zhang noted that when the Statistical Analysis Plan (SAP) for the Phase 3 study is prepared, the sponsor should consider adjusting the alpha for the secondary endpoints so that the overall type I error is controlled at (b) (4) The Division added that the SAP should be submitted to the Division for review well before any planned interim analysis.

6. Does the Division concur that, in addition to the Phase 2 studies, this single Phase 3 study DU176b-C-U301, provided that the results are sufficiently compelling, supports the proposed indication?

Preliminary Response:
A single study may be sufficient if the results are compelling.

Additional Discussion During Meeting:
No further discussion.

7. The statistical analysis plan (SAP) will propose a closed test procedure be conducted for analyzing the primary efficacy endpoint in accordance with the following priorities and (b) (4)

(b) (4)

Does the Division concur?

Preliminary Response:
The 30 mg qd group appears to be a mixture of the high-dose and low-dose groups. It is not clear what the purpose of including this group is. Interpretation of the results of this group will be difficult.

If a (b) (4) is used to control study-wise error rate, then there is no room to add a side branch to (b) (4); that is, all hypotheses under testing must be lined up (b) (4) As there are potentially (b) (4) in (b) (4), a proper control of the study-wise type I error requires a proper control of the type I error rate associated with the six comparisons. This error rate may not be properly controlled if you branch out to test superiority; for example, the type I error rate of falsely asserting superiority in at least one of the three dose regimen groups with your proposed test strategy can be up to 15%.

With such (b) (4) to proceed to testing superiority in order to control the type I error rate. Furthermore, the proposed criteria for (b) (4) at the interim analysis adds more difficulties in controlling the study-wise type I error rate. If the (b) (4) before the study ends for safety reasons, then the (b) (4) would still require non-inferiority for the (b) (4) in order to control the family-wise error rate. Also, if the (b) (4) non-inferiority is still required for all three groups before (b) (4) (b) (4) However, the (b) (4) may be illogical, though it will control the study-wise type I error rate associated with the six comparisons. We recommend that you consider other procedures that control the study-wise type I error rate. The simplest and cleanest way seems to be splitting alpha between the dose regimens so that testing non-inferiority and superiority can be based on the same confidence interval within each dose regimen group.

We look forward to additional discussion at the meeting.

Additional Discussion During Meeting:
The proposal to test all groups for superiority and (b) (4) poses problems. Assuming the (b) (4) is not stopped for safety, we will have no problem accepting a test, without correction for superiority, and the planned (b) (4) is also acceptable. We would probably have a problem if only the (b) (4) showed superiority. The Division noted that a clause of superiority ordinarily includes a replicated finding or a significance level of < 0.01 in one study. The sponsor asked if the trial would be more convincing if the data in all groups went in the same direction toward a win. Dr Temple responded that this could help. Lastly, the Division added that for secondary endpoints that were far different from the primary, a multiplicity adjustment would be needed (e.g., bone fractures).

8. If either DU-176b treatment group is (b) (4) due to safety concerns or other pre-specified reasons, then the analysis above will treat the study (b) (4) (b) (4).

(b) (4)
Does the Division concur?

Preliminary Response:
No. Please see response to Question 7.

Additional Discussion During Meeting:
It was noted that the (b) (4) may get dropped for major bleeding. The sponsor described the three types of major bleed as intracranial, fatal and greater than 2 gm/dl drop in hemoglobin. Dr. Stockbridge said that bleeding that causes a 2 g/dl drop in hemoglobin should not be used as (b) (4) . Dr. Temple agreed and cautioned against (b) (4) because it could also have greater effect on (b) (4) reduction. In addition, Dr. Stockbridge noted that if the (b) (4), the burden will be on the sponsor for explaining why the (b) (4) in people where this represents a (b) (4)

9. If the DU-176b 30 mg qd regimen is non-inferior to warfarin with regards to efficacy and has a safety profile comparable to or better than warfarin, then does the Division agree that the DU-176b 30 mg qd regimen may be recommended for use in the product labeling?

Preliminary Response:
Please see response to Question 7.

Additional Discussion During Meeting:
After the sponsor presented slides (attached as an appendix to the minutes), the proposal seemed reasonable to the Division.

10. If the criterion for non-inferiority is satisfied for any DU-176b regimen versus warfarin, then an analysis for superiority will be reported. Testing for superiority of any given DU-176b regimen will be performed even if another DU-176b regimen fails to show non-inferiority to warfarin. Does the Division concur?

Preliminary Response:
No. Please see response to Question 7.

Additional Discussion During Meeting:
Dr. Stockbridge said that the Division was hoping for a robust finding to support superiority. For example, a significance level of 0.01 is generally required for a single trial for a superiority claim, although a mortality claim can be supported by a higher p-value. The overall type I error should take both the primary and the secondary endpoints into account. The sponsor agreed to consider these comments.

11. The planned statistical analysis specifies that if the upper limit of the (b) (4)% confidence interval (CI) for the relative risk ratio (DU-176b regimen vs. warfarin) is below one, then superiority of the DU-176b regimen is shown. Does the Division agree that this statistical procedure is appropriate to demonstrate superiority?

Preliminary Response:
Please see response to Question 7.

Additional Discussion During Meeting:
Please see this subsection under Question #10 for a related response.

12. The primary efficacy endpoint analysis for the Per Protocol Analysis Set adopts an on-treatment approach. This analysis will include only events that occur while on study drug. Events that occur on days that a subject missed a dose will still count. Events that occur during a planned study drug interruption will not count. Does the Division concur with this Per Protocol analysis method? Does the Division agree with the Per Protocol analysis as supportive and the Intent-to-Treat (ITT) analysis as primary for the primary efficacy endpoint analysis?

    Preliminary Response:
    The results of the sensitivity Per Protocol analysis using "on treatment" approach need to be consistent with the results of the ITT analysis.

    The crossover rate (percentage of discontinued DU176b patients switching to warfarin) needs to be reported and may have serious implications on interpretability of NI results.

    Additional Discussion During Meeting:
    Dr. Stockbridge inquired whether ITT was the primary efficacy endpoint analysis. The sponsor confirmed that this was the case. The sponsor also agreed to consider the Division's preliminary response when finalizing their Phase 3 protocol, TIMI-48.

    The sponsor clarified that their per protocol analysis counts subjects (absent major protocol violations) only during periods while they were on treatment. (Although not well captured here, the choice of ITT or Per Protocol [on treatment] as the primary analysis is controversial. ITT preserves statistical properties of the randomized group, but a non-inferiority study can falsely conclude two groups are similar when neither is receiving effective therapy.)

13. Does the Division agree that the safety data expected to be available at the time of NDA submission adequately support the review, registration, and approval of DU-176b for the proposed indication? It is expected that > 11,000 subjects with AF will be exposed (median treatment duration of 24 months) to DU-176b at the recommended dosage regimen.

    Preliminary Response:
    The planned size of the safety database should be adequate to support registration.

    Additional Discussion During Meeting:
    No further discussion.

14. Does the Division agree to the process of serious adverse event (SAE) reporting proposed for study DU176b-C-U301 as described below and the reporting of serious unexpected adverse reactions to the Agency in a blinded manner (i.e., study drug will remain blinded)?
    The Sponsor proposes that all SAEs be promptly reported to the Sponsor regardless of causal relationship to study drug except for those SAEs meeting criteria for efficacy and safety endpoints because these endpoints are disease related and therefore expected. Adverse events (AEs) meeting both endpoint criteria and serious criteria should be submitted to the Sponsor as an SAE only if assessed by the Investigator as related (possibly, probably, or definitely) to the study drug. Does the Division concur?

    Preliminary Response:
    We agree that you do not need to report components of the primary and secondary endpoints as 7 or 15-day safety reports. Additionally, bleeding and some other cardiovascular events such as hospitalization for heart failure adverse events are expected in a trial of anticoagulant administration and so reporting

of individual events is not informative. The Data Safety Monitoring Committee is responsible for monitoring the frequency of expected adverse events to see if an unusual pattern of events is occurring. However, we are not clear about your proposal that investigators not report to you "expected" SAEs. Unless all SAEs are reported, the Data Safety Monitoring Committee will not be able to detect important imbalances in the occurrence of e.g. bleeding between treatment groups. Serious adverse events have a regulatory definition, and "expectedness" is not part of that definition.

Additional Discussion During Meeting:
We agreed that some commonly reported events should not be reported as 15-day reports. Reporting of 15-day SAEs should not include those that were part of the primary effectiveness endpoints, those being observed for safety (e.g., bleeding), or those expected in this particular patient population. Since the number of such SAEs is anticipated to be high, reporting all of them can overwhelm the investigator with uninformative "Dear Investigator" letters and inundate the Institutional Review Board (IRB). Prior to the initiation of Phase 3, the Division suggested that it would be beneficial to submit to the FDA a list of those events expected to occur frequently in this patient population and how the DMC or other internal body will examine those events for an excess rate in the DU-176b group. If the events are potentially therapy/outcome related, these events should not be unblinded, except to a DMC, but an event not part of the protocol endpoints where the patient has been discontinued can be unblinded.

15. Does the Division agree to DSPD's request for a (b) (4) of pediatric studies until after the safety and efficacy of DU-176b has been established for adults?

Preliminary Response:
Your request for a waiver will be reviewed by the Pediatric Review Committee (PeRC) once your NDA is submitted.

Additional Discussion During Meeting:
No further discussion.

16. Does the agency concur that the use of a standard point-of-care (POC) device manufactured by (b) (4) for INR measurements to adjust warfarin dosages and the use of a "sham INR" for blinding is appropriate for this registrational study?

Preliminary Response:
You propose having investigators adjust Coumadin doses. To claim DU_176b is non-inferior to warfarin, the management of warfarin dose in your trial must be at least as good as that in the historical trials used to estimate the treatment effect of warfarin. Further, subjects randomized to Coumadin may be exposed to unreasonable risk if the dose of Coumadin is not appropriately adjusted.

We suggest you propose a method, such as time in therapeutic range, to evaluate quality of investigators' Coumadin dosing. We further suggest you propose a method to monitor the adequacy of investigators' Coumadin dosing during the conduct of the trial. Finally we suggest that your analysis of your trial include a comparison of the adequacy Coumadin dosing to the expected using more than one measure, such as proportion of time in therapeutic range and proportion of time patients having significant deviations from therapeutic INR range. We also recommend that you provide feedback and guidance to investigators to ensure they adjust warfarin dosing appropriately.

Additional Discussion During Meeting:
The sponsor agreed and committed to instructing all investigators on appropriate warfarin dosing and to monitor the dosing throughout the trial.

Additional Comments:

1. The study protocol needs to clearly pre-specify the statistical test in the accelerated failure time model to be used in the primary efficacy analysis. Does this model assume the relative risk is the same at all time points? If so, is this a better or more reasonable model than the proportional hazards model? If not, at which time point is the relative risk defined for the primary analysis? Justification for why the accelerated failure time model is more appropriate for your application needs to be provided in detail.

2. Please explain why you plan to assess stroke severity using the Rankin scale at Day 5. Assessing severity too early may result in a systematic over-estimate of stroke severity.

3. Consider stratification by prior use of warfarin.

Additional Discussion During Meeting:

There was no further discussion regarding the above comments beyond that the sponsor will address them in the final protocol.

The sponsor asked the Division if submitting a Special Protocol Assessment (SPA) was recommended for this trial. Dr Stockbridge said that it was in the sponsor's best interest to submit the protocol as an SPA.

Per the sponsor, the 9-month monkey QC'd data is to be submitted the week of August 17th. The Division has already agreed to an expedited review of the final complete data set (minimum 30 day review) and to informally consult with DAIOP regarding any impact of DU-176b on eye function.

Dr. Grant added that the full QT study report should be submitted to the QT-IRT 45 days prior to first patient enrolled in the Phase 3 study.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Robert Temple, M.D.

Draft: ab 8/21/08
Final: ab 9/12/08

RD:
Fortney 8/22/08
Tornoe 8/25/08
Freidlin 8/26/08
Zhang 8/26/08
Lawrence 8/27/08
Hung 8/28/08
Tornoe 8/29/08
Grant 9/2/08
Marciniak 9/3/08

Fromm 9/4/08
Unger 9/3/08
Stockbridge 9/4/08
Temple 9/10/08

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name
IND 77254	DAIICHI SANKYO	DU 176B

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

/s/

ROBERT TEMPLE
09/24/2008

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
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Transmitted via mail:	DMorgan@dsus.com
Attention:	Doreen Morgan
Company Name:	Daiichi-Sankyo
Phone:	732.590.5198
Subject:	**IND 77,254 8Jul08 Type C Guidance Meeting Preliminary Responses**
Date:	1 July 2008
Pages including this sheet:	

From: **Alison Blaus**
Phone: **301-796-1138**
Fax: **301-796-9838**

*********PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

FDA Division of Cardiovascular and Renal Products Preliminary Responses

Sponsor:	Daiichi-Sankyo
Drug:	DU-176b
IND:	77,254
Date of request:	4 April 2008
Date request received:	8 April 2008
Date of confirmation:	10 April 2008
Date of meeting:	8 July 2008
Time:	2-3:30 pm
Place:	10903 New Hampshire Ave. Bldg #22, Room 1313 Silver Spring, MD 20993
Type/Classification:	C/Guidance
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting recorder:	Alison Blaus

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products
Maryann Gordon, M.D.	Medical Officer, Division of Cardio-Renal Drug Products
George Shashaty, M.D.	Medical Officer, Division of Hematology Products
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Patricia Harlow, Ph.D.	Pharmacologist
Peter Hinderling, M.D.	Clinical Pharmacology
Yaning Wang, Ph.D.	Pharmacometrics
Christoffer Tornoe, Ph.D.	Clinical Pharmacology
Federico Goodsaid, Ph.D.	Pharmacogenomics
Alison Blaus	Regulatory Health Project Manager, Cardio-Renal
Meg Pease-Fye	Regulatory Health Project Manager, Cardio-Renal
Diane Leaman	Regulatory Health Project Manager, Hematology

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 8, 2008 between Daiichi-Sankyo and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Alison Blaus), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you

would like FDA feedback arise prior to the meeting, contact Alison Blaus to discuss the possibility of including these for discussion at the meeting.

Questions for the Division:

1. Does the Agency agree that the completed, ongoing, and planned Non-clinical studies for DU-176b are adequate to support an NDA filing for the proposed indication?

   FDA Preliminary Response:
   No. Please see comments below under question 3 regarding the D21-2393.

2A. Does the FDA agree with the DSPD conclusion that the results of the 6 month interim data from the study, "Effects on Eye Function in Monkeys Treated Orally with DU-176b for 9 months', (b) (4)

   FDA Preliminary Response:
   The meeting package included data for pre-study, three months, and six months in a nine-month study in monkeys. Although no effect on ERG parameters was observed in females after treatment with DU176b, an equivocal signal for an effect on a-wave and b-wave amplitudes is observed at 6 months in males. Informally, a reviewer in DAIOP agreed that data at 9 months are needed to rule out an effect of DU-176b on eye function. (b) (4)

2B. DSPD plans to submit to FDA the 9 Month QC'd data from the study on August 15, 2008. Would the FDA agree to review this data in an expedited manner to permit DSPD to initiate Phase 3 in September 2008?

   FDA Preliminary Response:
   Appropriate review of the 9-month data will probably require a formal consult with DAIOP. The reviewer in DCaRP agrees to facilitate the consult with DAIOP. However, we request that that DCaRP be kept informed about the timing of the potential submission so that the reviewers in DCaRP and DAIOP can plan for this expedited review. We request a minimum of 30 days for this review.

3. Since D21-2393, a human disproportionate metabolite, caused chromosomal aberrations in CHL cells at high concentrations (1250 µg/mL or higher), a single and 14-day repeat dose in vivo micronucleus assay in rats, and a polyploidy test in human lymphocytes were initiated. If the results of the additional testing are indicate that D21-2393 is considered unlikely to have genotoxic risk *in vivo* as is for the parent compound DU-176b, does the Agency agree that this is sufficient to characterize the genotoxic potential of D21-2393 and to initiate the Phase 3 study?

   FDA Preliminary Response:
   Based on the data in the meeting package, D21-2393 is not a human disproportionate metabolite, but essentially a human specific metabolite. The studies conducted and in progress to characterize the genotoxic potential of D21-2393 are adequate to initiate a Phase 3 study, if D21-2393 is found unlikely to have genotoxic risk in vivo. However, to support NDA filing, additional general and reproductive toxicology testing of D21-2393 are necessary according to the CDER Guidance Safety Testing of Drug Metabolites (Feb. 2008).

4A. Does the Agency agree that the current clinical pharmacology studies and the data generated to-date to characterize the Pharmacokinetics/Pharmacodynamics (PK/PD) profile of DU-176b are sufficient to start the Phase 3 study in patients with atrial fibrillation?

FDA Preliminary Response:
No. The results of study PRT018 in patients with AF are not available. Thus, the PKPD of DU-176b are not characterized and the therapeutic regimens for Phase 3 are undetermined.

4B. Does the agency agree that the clinical pharmacology program (completed, on-going and planned studies) is adequate to support review of the NDA?

FDA Preliminary Response:
Yes, provided the potential of DU-176b to induce relevant enzymes and to inhibit P-gp is being determmined and the observed spontaneous hydrolysis of DU-176b to D21-3231 can be controlled in future studies and the extent of D21-3231 in past studies can be quantified and shown to be minor. Can generation of D21-2393 by spontaneous hydrolysis be excluded?

5. Does the agency agree with DSPD that the Thorough QTc study (PRT021) results, along with the Nonclinical data and the PopPKPD analyses, confirm that there is negligible potential for QTc liability associated with DU-176b?

FDA Preliminary Response:
Yes

6. Does the agency agree that the effect of renal insufficiency on the disposition of DU-176 is adequately characterized based on the renal impairment study (U120) results and the PopPK analysis?

FDA Preliminary Response:
Yes

7. Does the Agency agree that the metabolite D21-2393 has been adequately characterized and evaluated in non-clinical and in the clinical pharmacology program and that further measurement and evaluation of this metabolite in the Phase 3 is not necessary?

FDA Preliminary Response:
No. Please see comments above under question 3 regarding the D21-2393.

8. The metabolite D21-3231 is present at low exposure in both normal volunteers (< 10%) and patients with renal impairment (up to 21%).The safety margin of this metabolite is adequate based on high exposures in toxicological (rat/monkey) species. Does the Agency agree that the metabolite D21-3231 has been adequately characterized and evaluated in non-clinical and in the clinical pharmacology program and that further measurement and evaluation of this metabolite in the Phase 3 study is not necessary?

FDA Preliminary Response:
Yes

9. Does the Agency agree with DSPD PopPKPD models as described in the background information and in the attached technical report (Appendix B)? Does FDA have any additional suggestions?

FDA Preliminary Response:

In general, the developed PK/PD models are reasonable. The PK model predictions [redacted] (Figures 8 and 9 in technical report). The PK model appears to [redacted] (e.g. [redacted]. Furthermore, instead of estimating the [redacted] You may consider simplifying your model by [redacted] include clinically significant covariates (e.g. those with more than 20 % effect on PK parameters). Finally, it is not clear from the document how the developed PD models are going to be used for dose selection/adjustment.

10. The doses for the Phase 3 AF study will be based on the PRT018 results. DSPD's strategy involves exclusion of doses or regimens that result: 1) in higher bleeding relative to warfarin and 2) which has less effect on coagulation biomarkers relative to warfarin. PopPKPD analysis will be integral to the selection of the optimal doses and will include various biomarkers and covariates in this extensive analysis.

    Does FDA agree with the DSPD's proposal to select doses for the Phase 3 AF study based on this strategy and the PopPKPD?

FDA Preliminary Response:

We agree with the strategy in general. However, the identified exposure-response relationships for VTE and bleeds are very shallow (Figures 19-21 in technical report) and it is difficult to define a therapeutic window for DU-176b based on the limited number of patients/events in the Phase 2b study. The modeling should be repeated when the results form the PRT018 are available.

Additional Comments:

Even though biomarker-based dose selection is reasonable, we have seen cases where the clinical efficacy endpoint did not achieve non-inferiority goal against warfarin while D-dimer endpoint is superior to warfarin. You should keep this in mind when selecting dose based on a D-dimer related biomarker.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Norman Stockbridge, M.D., Ph.D.

Draft: AB -23 June 2008
Final: AB -1 July 2008

RD:
DeFelice6/23/08
Harlow 6/23/08
Hinderling 6/24/08
Wang 6/24/08
Gordon 6-25-08
Shashaty 6/25/08
Stockbridge 7/1/08

Linked Applications	Sponsor Name	Drug Name
IND 77254	DAIICHI SANKYO	DU 176B

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

/s/

NORMAN L STOCKBRIDGE
07/01/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 77,254

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, Pharm.D, M.S., Executive Director
Regulatory Affairs
399 Thornall St.
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DU-176b.

We acknowledge receipt of your April 21, 2008, request on April 23, 2008, for a special clinical protocol assessment. The protocol is titled, "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 – Lowered stroke risk in atrial fibrillation with Inhibition of activated Factor Ten (LIFT)".

After considering your request, we have determined that the submission is not appropriate for a special protocol assessment at this time. Pursuant to the April 24, 2008, telephone conversation between Daiichi-Sankyo and Ms. Alison Blaus of our Division, we note that you will be possibly requesting an end of phase 2 meeting in the near future.

As explained in FDA's May 2002 "*Guidance for Industry: Special Protocol Assessment*," "...for special protocol assessment of a protocol for a clinical trial that will form the primary basis of an efficacy claim in an NDA or BLA, the sponsor should have had a meeting with the review division so that the division is aware of both the developmental context in which the protocol is being reviewed and the questions that are to be answered." Thus, we believe that the interests of the clinical development program would be better served if you delayed submission of the protocol for special protocol assessment until after you have received our advice at the end of phase 2 meeting. At that point, we believe you will be better informed to enable planning of the study, and we will be in a better position to advise you.

We recommend that you refer to the "*Guidance for Industry: Special Protocol Assessment*" for information on the types of protocols that qualify for this program. Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm.

If you have any questions, please call Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 77254	DAIICHI SANKYO	DU 176B

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

/s/

NORMAN L STOCKBRIDGE
04/28/2008

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316

LATE-CYCLE MEETING MINUTES

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street, 10th Floor
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) dated January 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 8, 2014. A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call the following Regulatory Project Managers:
For NDA 206316/Original 1 – Alison Blaus, RAC at (301) 796-1138
For NDA 206316/Original 2 (b) (4) – Janet Higgins at (240) 402-0330

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 8, 2014 from 0930 – 1100 EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903
Application Number: NDA 206316
Product Name: SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets
Proposed Indications:
1. Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Original 1)
2. Treatment of deep vein thrombosis and pulmonary embolism (Original 2)

(b) (4)

Applicant Name: Daiichi Sankyo Inc.
Meeting Chair: Martin Rose, MD and Kathy Robie-Suh, MD, PhD
Meeting Recorder: Alison Blaus, RAC

FDA ATTENDEES

* *Office of New Drugs, Office of Drug Evaluation I*	
Ellis Unger, MD	Director
Robert Temple, MD	Deputy Director
* *Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products*	
Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Safety Deputy Director
Martin Rose, MD, JD	Cross-Discipline Team Leader (CDTL) (Original 1)
Melanie Blank, MD	Clinical Reviewer (Original 1)
Tzu-Yun McDowell, PhD	Clinical Reviewer (Original 1)
Nhi Beasley, PharmD	Clinical Reviewer
Thomas Papoian, PhD	Team Leader, Pharmacology/Toxicology
Baichun Yang, Ph.D.	Pharmacology/Toxicology Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Project Manager
Lori Wachter, RN, RAC	Safety Project Manager
* *Office of New Drugs, Office of Hematology and Oncology Products, Division of Hematology Products*	
Ann Farrell, MD	Director
Robert Kane, MD	Safety Deputy Director
Kathy Robie-Suh, MD, PhD	Cross-Discipline Team Leader (CDTL) (Original 2 (b) (4)
Saleh Ayache, MD	Clinical Reviewer (Original 2 (b) (4)
Janet Higgins	Regulatory Project Manager
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, PhD	Team Leader – Clinical Pharmacology
Divya Menon-Andersen, PhD	Reviewer
Young-Jin Moon, PhD	Reviewer
Jeff Florian, PhD	Acting Team Leader – Pharmacometrics

Justin Earp, PhD	Pharmacometrics Reviewer
* *Office of Biostatistics*	
Lei Nie, PhD	Team Leader – Statistics (Original 2 (b) (4)
John Lawrence, Ph.D.	Statistician (Original 1)
Yun Wang, PhD	Statistician (Original 2 (b) (4)
* *Office of New Drug Quality Assessment*	
Janice Brown, MS	Branch Chief
Sandra Suarez, PhD	Biopharmaceutics
* *Office of Surveillance and Epidemiology*	
Doris Auth, PharmD	DRISK Team Leader
Kimberly Lehrfield	DRISK Team Leader
Cathy Miller, MPH, BSN	DRISK Reviewer (Original 1
Carolyn Yancey, MD	DRISK Reviewer (Original 2 (b) (4)
Anne Tobenkin	Pharmacovigilence
* *Office of Scientific Investigations Good Clinical Practice Assessment Branch*	
Sharon K. Gershon, PharmD	Reviewer
* *Office of Medical Policy, Division of Medical Policy Initiatives*	
Sharon Mills, BSN, RN, CCRP	Patient Labeling
* *Office of Prescription Drug Promotion* (*OPDP*)	
Zarna Patel, PharmD	Reviewer
* *Office of Executive Programs, Division of Advisory Committee & Consultant Management*	
Yvette Waples	Team Leader
Kristina Toliver, PharmD	Acting Designated Federal Officer, CRDAC

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou	Independent Assessor

DAIICHI SANKYO ATTENDEES

Glenn Gormley, MD, PhD	Senior Executive Officer and Global Head of R&D
Mahmoud Ghazzi, MD, PhD	Executive Vice President, Global Head of Development,
Michele Mercuri, MD, PhD	Senior Vice President Clinical Development Americas, and Chief Medical Advisor
Kimberly Stranick, MS, PhD	Vice President, Regulatory Affairs
Doreen Morgan, Pharm.D., MS	Executive Director, Regulatory Affairs
Linda Nelson, PhD	Director, Regulatory Affairs-CMC
Diane Benezra-Kurshan, MD, MPH	Senior Director, Regulatory Affairs-Labeling
John Castellana, PhD	Vice President, Biostatistics and Data Operations
Kenneth Truitt, MD	VP, Translational Medicine and Clinical Pharmacology
Michael Grosso, MD, FACS	Executive Director, Clinical Development- Cardiovascular
Allen Feldman, MD, MPH	Vice President, Clinical Safety and Pharmacovigilance
Youngsook Choi, MD	Senior Director, Clinical Safety and Pharmacovigilance
Hans Lanz, MD	Executive Director, Clinical Development-Cardiovascular
Dolly Parasrampuria, PhD	Senior Director, Translational Medicine and Clinical Pharmacology
Martins Adeyemo, PhD, DABT	Senior Director, Medicinal Safety, Non-clinical Development
John Kappelhof, MBA, PMP	Executive Director, Global Project Management & Leadership
Minggao Shi, PhD	Senior Director, Biostatistics

1.0 BACKGROUND

NDA 206316 was submitted on January 5, 2014 for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets

Proposed indication(s):
1. Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Original 1)
2. Treatment of deep vein thrombosis and pulmonary embolism (Original 2)

(b) (4)

PDUFA goal date: January 8, 2015

FDA issued a Background Package in preparation for this meeting on September 29, 2014.

2.0 DISCUSSION

DISCUSSION OF SUBSTANTIVE REVIEW ISSUES

- ***Chemistry, Manufacturing, and Controls (CMC)***

CMC review conclusion is pending an "overall acceptability" decision to be made by the Office of Compliance.

Discussion during the Meeting
No further discussion at the meeting.

- ***ONDQA - Biopharmaceutics***

An approval action with a post-marketing commitment is being recommended, provided the inspection report from OSI, which is currently pending, does not report any objections for accepting the analytical and clinical data from BE study A-U142.

In a teleconference dated September 4, 2014, and in a submission dated September 5, 2104, the Applicant agreed to a post-marketing commitment to be fulfilled within 15 months from action date for: i) development of a new dissolution method, which shows greater discriminating ability (b) (4) and ii) setting of the final dissolution acceptance criterion of their drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches. The details of the post-marketing letter are pending.

Discussion during the Meeting
Dr. Suarez committed to providing the details of the study via email as well as the desired timeline for the Applicant's review and commitment.

Post-Meeting Note
A description of the PMC and the desired timelines was sent to the Applicant on October 22, 2014 for their review and concurrence. Once mutually agreed, the Applicant will submit their concurrence (with the description and timelines) to the NDA.

- ***Pharmacology & Toxicology***

  There are no substantive review issues at this time.

  Discussion during the Meeting
  No further discussion at the meeting.

- ***Clinical Pharmacology- Atrial Fibrillation (original-1)***

  1. ENGAGE AF met its pre-specified non-inferiority criteria compared to warfarin for the primary efficacy endpoint: first adjudicated stroke/SEE (mITT population, on-treatment period) [Edoxaban 30 mg: HR: 1.07 (0.87-1.31), $p < 0.01$ and edoxaban 60 mg: HR: 0.79 (0.63-0.99), $p < 0.0001$]. However, in the edoxaban 30 mg (15 mg DA) group, results were not favorable for ischemic stroke [HR (95% CI): 1.54 (1.25-1.9), nominal $p < 0.0001$] and disabling stroke [HR (95% CI): 1.36 (0.91-2.03)]. For this reason, you are seeking approval to market only the 60-mg dose (30 mg DA) of edoxaban; we concur with this choice.

     As we have discussed with you previously, our central review issue continues to be inadequate efficacy in the subgroup of subjects with normal renal function (CrCL≥ 80 mL/min). For these subjects, the HR for first stroke/SEE for edoxaban 60 mg (30 mg DA) compared to warfarin was 1.41 (95% CI: 0.97-2.05). The nominal p-values for subgroup interaction were highly statistically significant ($p< 0.001$ for the 60-mg dose and < 0.01 for the 30-mg dose). Less favorable results for the primary endpoint, its components, and CV death were consistently observed across edoxaban dose groups in subjects with CrCL≥80 mL/min.

     Our analyses indicate that the observed poorer outcomes relative to warfarin are closely correlated with lower edoxaban trough concentrations ($C_{troughs}$) in patients with normal renal function, and so we believe the reduced concentrations are determinative. This conclusion is also supported by the observation that the most favorable reduction in stroke rate compared to warfarin [HR (95%CI): 0.53 (0.40 – 0.70)] was observed in patients with mild renal dysfunction (CrCL ≥50 – < 80 mL/min), the sub-group with highest edoxaban exposure in ENGAGE AF. Also supportive is the observation that bleeding rates (relative to warfarin) were lower in edoxaban patients with normal renal function [HR (95% CI): 0.71 (0.55 – 0.90)] as compared to that in patients with mild renal dysfunction [HR (95% CI): 0.90 (0.75 – 1.08)].

     A formal exposure–response analysis using a multivariate Cox Proportional Hazards model identified edoxaban trough concentration, among others, as a significant predictor of efficacy and safety. Similar relationships have been found for other thrombotic and safety events of interest, including ischemic strokes, hemorrhagic strokes, life-threatening/fatal bleeds, and major gastrointestinal bleeds. In general, these relationships project a decrease in efficacy event rates with increasing edoxaban doses and an increase in bleeding rates with increasing

edoxaban doses. Projected relative risk estimates for the primary efficacy and safety endpoints by doses corresponding to exposure within the current clinical trial experience (< 95th percentile of observed $C_{troughs}$ in ENGAGE AF) are presented in the table below. A similar approach could also be applied to patients with moderate impairment of renal function (CrCL ≥30 – <50 mL/min) to further reduce the risk of stroke/SEE while projecting the increase in bleeding risk.

Table: Risk ratio based on stroke/SEE and major bleed event rates projected for edoxaban with doses greater than that studied in ENGAGE AF. Risk ratios are presented relative to the observed event rate for warfarin and grouped by renal function category.

Endpoint	Renal Function Category	Comparison[#]	Risk Ratio
Stroke/SEE	Normal (CrCL≥ 80mL/min)	Edoxaban 60 vs Warfarin*	1.41
		Edoxaban 75 vs Warfarin	1.12
		Edoxaban 90 vs Warfarin	1.05
	Moderately Impaired (CrCL ≥30 – <50 mL/min)	Edoxaban 30 vs Warfarin*	0.88
		Edoxaban 37.5 vs Warfarin	0.74
		Edoxaban 45 vs Warfarin	0.71
Major Bleed	Normal (CrCL≥ 80mL/min)	Edoxaban 60 vs Warfarin*	0.71
		Edoxaban 75 vs Warfarin	0.91
		Edoxaban 90 vs Warfarin	1.19
	Moderately Impaired (CrCL ≥30 – <50 mL/min)	Edoxaban 30 vs Warfarin*	0.75
		Edoxaban 37.5 vs Warfarin	0.79
		Edoxaban 45 vs Warfarin	1.10

*Observed Hazard Ratio
[#]Edoxaban dose listed for patients with moderate impairment of renal function denotes the dose administered after taking into account decreased renal function (i.e., subjects with moderate impairment of renal function are administered 50% of the overall treatment dose).

You have indicated that you believe that the discrepancy in observed outcomes among subjects with differing levels of renal function may be because of better outcomes in warfarin subjects with normal renal function. While outcomes in the warfarin arm were better in the normal renal function subgroup compared to outcomes in subjects with renal impairment, we believe that finding irrelevant. Similar results were observed for warfarin in this subgroup in trials of other NOACs. Comparisons of outcomes between subjects randomized to edoxaban and warfarin are more useful than nonrandomized comparison of results within warfarin subjects.

2. We are unlikely to support adjusting dose based on based on (b) (4)

3. Co-administration of rifampin results in ~ 40% loss of total systemic edoxaban exposure (AUC). While an increase in systemic exposure to its equipotent active metabolite D21-2393

makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (C_{max}) to D21-2393. At trough (end of inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined. Loss in exposure is considered detrimental based on the identified exposure-response efficacy relationships and difference in response rates between the two edoxaban treatment arms (30 mg QD versus 60 mg QD). Hence, we are likely to recommend that edoxaban should not be co-administered with a P-gp inducer.

4. Patients with moderately impaired hepatic function (Child-Pugh B) may have intrinsic coagulation abnormalities. Hence we do not believe the results of exposure-response analysis in patients without hepatic impairment should be extrapolated to determine a dose in patients with hepatic impairment. Labels for previously approved Factor Xa inhibitors do not make a dosing recommendation for patients with moderately impaired hepatic function.

5. Dosing recommendations and labeling pertaining to intrinsic and extrinsic factors may differ between the indications being sought because of differences in the Phase 3 programs. To illustrate, the anti-arrhythmic drug dronedarone was prohibited in Hokusai VTE, whereas dronedarone use required an edoxaban dose reduction in ENGAGE-AF. Different dosing recommendations may be necessary in this instance.

Discussion during the Meeting

Dr. Earp pointed out that most of the abovementioned comments were already conveyed to the Applicant at previous meetings, with the exception of the dose adjustment (b) (4) The Applicant requested the Agency's modeling parameters/methodology for final ER models and to include SEE, major bleed and ischemic stroke. The FDA agreed to provide the parameters and methodology.

Post-Meeting Note

Instead of providing the parameters and methodology, the pharmacometrics team directed the Applicant to the Advisory Committee (AC) briefing book, which included their review and these items. Upon reviewing the AC book, the Applicant did not have any further questions or requests.

- ***Clinical – Atrial Fibrillation (ORIG-1)***

1. Our major concern is that analysis of exposure and outcomes in subjects with normal renal function suggests that lower exposures in this subgroup resulted in an unacceptable reduction in efficacy. We note that there is no unmet medical need because two other drugs proven superior to warfarin are approved for the same indication. Edoxaban offers no obvious advantage over those drugs and at the dose studied in ENGAGE AF appears to offer less protection against stroke in patients with normal renal function. Hence we believe that our concern about the efficacy of edoxaban in patients with normal renal function represents a serious impediment to approvability for patients with normal renal function, and possibly all patients. We have concerns about recommending a dose higher than that studied in ENGAGE-AF for patients with normal renal function based solely on an analysis of exposure and outcomes in ENGAGE-AF patients with mildly impaired renal function. Understanding the clinical effects of an increased dose may require an additional trial.

   Additionally, we are concerned that extrapolating bleeding outcomes solely on the basis of systemic edoxaban exposures may underestimate bleeding risk. If local gastrointestinal (GI)

exposure affects the risk of GI bleeding, then the risk of GI bleeding consequent to administering a dose of edoxaban higher than studied in ENGAGE-AF will be higher than suggested by modeling based solely on systemic exposure. It may be necessary to perform a clinical trial to assess the risk of bleeding associated with an edoxaban dose greater than 60 mg daily.

2. The following information may need to be included in the label:

   (1) Administration of edoxaban results in small changes in creatinine clearance and serum creatinine

   (2) A description of the imbalance in interstitial lung disease (ILD) between the groups. Our review of your recent submitted information with regard to ILD is still ongoing.

Discussion during the Meeting

Dr. Blank explained that she continues to have concern about patients with normal renal function who are administered the 60-mg dose. She also noted that she is beginning to analyze the data looking at SEE and ischemic stroke separately from hemorrhagic strokes instead of combining all strokes together, a strategy also endorsed by Dr Temple, as the dose-response for the two kinds of strokes appears quite different. Dr. Blank also pointed out that this study questions the concept that one dose fits all for this indication and suggests that it would be advantageous to be able to measure drug levels and titrate the dose accordingly. Dr. Unger added that having a test to inform dosing would be a large advantage and should be considered.

Dr. McDowell noted that there were no safety issues that affect approvability, but mentioned that the reviewers are considering including the imbalanced rates of interstitial lung disease SAEs in the label. FDA and the Applicant plan to discuss this further in another meeting.

Dr. Temple said that we are learning about these drugs as we examine submitted data, and acknowledged that showing an advantage over well-managed warfarin, i.e., as warfarin was used in ENAGAGE, for thromboembolic strokes is difficult. Although edoxaban may have in fact shown such an advantage in the mild renal impairment group. The Applicant noted that they set up a carefully designed and rigorous trial and changing the hypothesis (from all patients) after it is completed was less than ideal. The Applicant added that they think hemorrhagic stroke is important to patients too and should be described in labeling. Dr. Temple agreed that hemorrhagic stroke is just as important to patients and clinicians as ischemic stroke, and agreed that the NOACs all seem to have an important advantage on that endpoint. He explained that FDA thought both kinds of stroke were critical but that dose-finding needs to consider ischemic and hemorrhagic strokes separately. So far, it appears that all NOACs reduce hemorrhagic strokes compared to warfarin, so that it is critical to optimize effects on thrombotic stroke, while staying below doses that cause important increases in bleeding, including both hemorrhagic stroke and other bleeding. It probably would make sense to consider the non-inferiority analysis both for all-stroke and thromboembolic stroke, and the non-inferiority margins would be similar (and large) for both, with M2 in the neighborhood of 1.38. But, it seems likely that proper dosing may yield effects on thromboembolic stroke that are better than warfarin if the correct dose were found.

- ***Biostatistics – Atrial Fibrillation (ORIG-1)***

  There are no substantive review issues at this time.

Discussion during the Meeting
No further discussion at the meeting.

- ***Clinical & Biostatistics – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)***
(b) (4)

(b) (4)

Discussion during the Meeting
Dr. Farrell noted that the FDA and the Applicant appeared in agreement regarding the indication sought under ORIG-2, (b) (4) The applicant explained that their viewpoint might not be too far off from the FDA and would like to propose new labeling language to the Agency along with their rationale. The Agency agreed to review this new labeling language and rationale and to contact the Applicant if there is need for clarification and or if a teleconference is deemed necessary.

DISCUSSION OF UPCOMING ADVISORY COMMITTEE MEETING

Date of AC meeting: October 30, 2014
Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: October 9, 2014

Potential questions and discussion topics for AC Meeting are as follows (the questions below were the proposed questions at the time of the Late Cycle Meeting):

1. DISCUSSION: Please comment on your interpretation of the primary endpoint, ischemic stroke, and bleeding results in the various subgroups based on renal function in the ENGAGE AF trial:

   a) Do you believe the observed differences in the effects of treatment among the renal function subgroups should be attributed to the play of chance?

   b) If not, do you believe the differences in outcomes should be attributed to differences in exposure to edoxaban among the subgroups?

   c) If there is uncertainty in your assessment, how uncertain are you and why?

   d) Do you believe that the observed discrepancies in outcomes among subgroups based on renal function in the ENGAGE AF trial are an important consideration in the approvability of edoxaban to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation?

2. DISCUSSION: Is it appropriate to consider recommending a dose for patients with well-preserved renal function or moderate renal impairment based on analysis of the relationship between serum concentration of edoxaban and major efficacy and safety outcomes in ENGAGE-AF subjects with mild renal impairment?

   Note: While recommending unstudied doses in labeling to account for factors that change exposure (e.g., renal impairment and drug-drug interactions) is routine, exposure matching would result in a recommending a dose in labeling higher than any dose studied in Phase 2 or Phase 3 studies of edoxaban.

3. DISCUSSION: Is it appropriate to consider approving edoxaban with labeling that discourages use in those with well-preserved renal function if one were not convinced that an appropriate dose for this patient subgroup had been determined?

   Note: Patients with well-preserved renal function constitute a minority of patients with non-valvular atrial fibrillation who are candidates for anticoagulation according to the ACC/AHA/ESC 2006 Guidelines. However, such labeling would be unprecedented.

4. VOTE: Approval of edoxaban for the reduction of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. In considering options a, b and c, you should assume that edoxaban will be approved for patients with moderately impaired renal function with a recommended dose lower than 60 mg.

   a) Edoxaban should be approved with a 60 mg dose recommended in the label for patients with well-preserved or mildly impaired renal function.
   b) Edoxaban should be approved, but a higher dose than 60 mg should be recommended in the label for patients with well-preserved renal function.
   c) Edoxaban should be approved, but only for patients with mild and moderate renal impairment.
   d) Edoxaban should not be approved at this time.

5. DISCUSSION: If edoxaban is approved, should the Applicant perform additional studies to support dosing instructions? Please offer advice about the goals, control groups, and primary endpoints of such studies.

6. DISCUSSION: If edoxaban is not approved, what additional studies should the Applicant perform to support approval? Please offer advice about the goals, control groups, and primary endpoints of such studies.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location: http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

Discussion during the Meeting

Dr. Rose explained that the reviews included in the AC Briefing Book will provide the data to answer these questions. Although these questions may evolve, there will be no new issues raised, other than those already mentioned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

- ***Atrial Fibrillation (ORIG-1)***

  Edoxaban is currently under review for the proposed indication of the reduction in the risk of stroke and system embolism in patients with nonvalvular atrial fibrillation (AF). The Division of Risk Management (DRISK) review team for this indication cannot make final determinations about the need for a Risk Evaluation and Mitigation Strategy (REMS) for edoxaban until the risk-benefit profile is further discussed at the October 30, 2014 meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC). Following AC discussions, including the committee's recommendations about the safety and efficacy profile of edoxaban, DRISK will make a recommendation on risk management strategies for the product.

  Discussion during the Meeting
  The Agency said that no final determination has been made at this point and will be awaiting the outcome of the subgroup discussion at the AC. It was added that no DRISK review will be in the AC Briefing Book, no DRISK slides will be presented, and no questions posed regarding a REMS.

- ***Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)*** (b) (4)

  No issues that would require a REMS for the VTE indication have been identified to date.

  Discussion during the Meeting
  No further discussion at the meeting.

POSTMARKETING REQUIREMENTS/POSTMARKETING COMMITMENTS

Discussion during the Meeting

- PMC for dissolution – Please see the discussion under Substantive review issues - ONDQA – Biopharmaceutics.
- Dr. Farrell explained that anticoagulation in the pediatric population was important, and an oral formulation could be beneficial. She said that the Division will work with the Applicant to discuss the PMR deferral description and timelines. Dr. Stockbridge said that the waiver was still acceptable for the atrial fibrillation indication.

MAJOR LABELING ISSUES

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

- **Pharmacology & Toxicology**

  Some information of nonclinical studies was not included or not correctly interpreted in the labeling. We suggest following changes for sections 8.1, 8.2, 8.4, 12.1, 13.1, and 13.2 - (a) delete (b) (4) since there is not enough data to support; (b) use AUC to make exposure comparison between humans and animals whenever animal AUC is available; (c) include information about delayed avoidance response (a learning test) in female offspring (rats), lower body weight in

juvenile rats, high mortality and liver findings in 2-year rat study; (d) provide separate information for males and females in the carcinogenesis section. Suggestions for labeling are here –

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SAVAYSA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Embryo-fetal development studies were conducted in pregnant rats and rabbits during the period of organogenesis. In rats, no teratogenic effects were seen when edoxaban was administered orally at doses up to 300 mg/kg/day, or 49-times the human dose of 60 mg/day [(b) (4)] body surface area [(b) (4)] Increased post-implantation loss occurred at 300 mg/kg/day, but this effect may be secondary to the maternal vaginal hemorrhage seen at this dose. In rabbits, no teratogenic effects were seen at doses up to 600 mg/kg/day (49-times the human exposure at a dose of 60 mg/day when based on AUC). Embryo-fetal toxicities occurred at maternally toxic doses, and included absent or small fetal gallbladder at 600 mg/kg/day, and increased post-implantation loss, increased spontaneous abortion, and decreased live fetuses and fetal weight at doses equal to or greater than 200 mg/kg/day, which is equal to or greater than 20-times the human exposure.

In a rat pre- and post-natal developmental study, edoxaban was administered orally during the period of organogenesis and through lactation day 20 at doses up to 30 mg/kg/day, which is up to 3-times the human exposure when based on AUC. Vaginal bleeding in pregnant rats and delayed avoidance response (a learning test) in female offspring were seen at 30 mg/kg/day.

8.2 Labor and Delivery

Safety and effectiveness of SAVAYSA during labor and delivery have not been studied in clinical trials. The risks of bleeding should be balanced with the risk of thrombotic events when considering the use of SAVAYSA in this setting.

[(b) (4)]

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. [(b) (4)]

12.1. Mechanism of Action

Edoxaban is a [redacted] selective [redacted] inhibitor of [redacted] FXa, [redacted] It does not require antithrombin III for antithrombotic activity. Edoxaban inhibits free FXa, and prothrombinase activity and [redacted] inhibits thrombin-induced platelet aggregation. Inhibition of FXa in the coagulation cascade reduces thrombin generation [redacted] and reduces [redacted] thrombus formation.

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13. Nonclinical Toxicology

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Edoxaban was not carcinogenic when administered daily to mice and rats by oral gavage for up to 104 weeks. The highest dose tested (500 mg/kg/day) in male and female mice was 3 and 6 times, respectively, the human exposure (AUC) at the human dose of 60 mg/day, and the highest doses tested in male (600/400 mg/kg/day) and female (200 mg/kg/day) rats were 8 and [redacted] times, respectively, the human exposure at the human dose of 60 mg/day.

Edoxaban and its human-specific metabolite, M-4, were genotoxic in *in vitro* chromosomal aberration tests but were not genotoxic in the in vitro bacterial reverse mutation (Ames test), in *in vitro* human lymphocytes micronucleus test, in in vivo rat bone marrow micronucleus test, *in vivo* rat liver micronucleus test, and in in vivo unscheduled DNA synthesis tests.

Edoxaban showed no effects on fertility and early embryonic development in rats at doses of up to 1000 mg/kg/day (162 times the human dose of 60 mg/day [redacted] body surface area).

[redacted]

Discussion during the Meeting
No further discussion at the meeting.

Post-meeting Note
It should be noted that additional changes to the nonclinical portion of the label are pending as follows:

1. Section 13.1: Change one number: "The highest dose tested (500 mg/kg/day) in male and female mice was 3 and 6 times, respectively, the human exposure (AUC) at the human dose of 60 mg/day, and the highest doses tested in male (600/400 mg/kg/day) and female (200 mg/kg/day) rats were 8 and [redacted] times, respectively, the human exposure at the human dose of 60 mg/day."

   To "The highest dose tested (500 mg/kg/day) in male and female mice was 3 and 6 times, respectively, the human exposure (AUC) at the human dose of 60 mg/day, and the

highest doses tested in male (600/400 mg/kg/day) and female (200 mg/kg/day) rats were 8 and **14** times, respectively, the human exposure at the human dose of 60 mg/day.

2. Delete (b) (4)

- ***Clinical & Biostatistics – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)***
(b) (4)

1. You seek the full approval of Edoxaban for the indications: treatment of DVT and PE, (b) (4) We find support for treatment of DVT and PE (b) (4)

1. (b) (4)

2. (b) (4)

3. (b) (4)

4. In Figure 14.3 in the labeling, (b) (4) which makes the figure confusing to read. The figure should be revised to show cumulative incidence rate for recurrent VTE or VTE-related death based on mITT population for overall study period only.

5. (b) (4)

Discussion during the Meeting
Please see the Clinical & Biostatistics (ORIG-2 (b) (4) under substantive review issues.

WRAP-UP AND ACTION ITEMS

This application has not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

NORMAN L STOCKBRIDGE
11/07/2014

ANN T FARRELL
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316/Original 1
NDA 206316/Original 2
(b) (4)

LATE CYCLE MEETING
BACKGROUND PACKAGE

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 8, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please call the following Regulatory Project Managers:
For NDA 206316/Original 1 – Alison Blaus, RAC at (301) 796-1138
For NDA 206316/Original 2 (b) (4) – Janet Higgins at (240) 402-0330

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 8, 2014 from 0930 – 1100 EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903
Application Number: NDA 206316
Product Name: SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets
Proposed Indications:
1. Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Original 1)
2. Treatment of deep vein thrombosis and pulmonary embolism (Original 2)

[redacted] (b) (4)

Applicant Name: Daiichi Sankyo Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

- ***Chemistry, Manufacturing, and Controls (CMC)***

  CMC review conclusion is pending an "overall acceptability" decision to be made by the Office of Compliance.

- ***ONDQA - Biopharmaceutics***

  An approval action with a post-marketing commitment is being recommended, provided the inspection report from OSI, which is currently pending, does not report any objections for accepting the analytical and clinical data from BE study A-U142 .

  In a teleconference dated September 4, 2014, and in a submission dated September 5, 2104, the applicant agreed to a post-marketing commitment to be fulfilled within 15 months from action date for: i) development of a new dissolution method, which shows greater discriminating ability (b) (4) and ii) setting of the final dissolution acceptance criterion of their drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches. The details of the post-marketing letter are pending.

- ***Pharmacology & Toxicology***

  There are no substantive review issues at this time.

- ***Clinical Pharmacology- Atrial Fibrillation (ORIG-1)***

  1. ENGAGE AF met its pre-specified non-inferiority criteria compared to warfarin for the primary efficacy endpoint: first adjudicated stroke/SEE (mITT population, on treatment period) (Edoxaban 30 mg: HR: 1.07 (0.87-1.31), $p < 0.01$ and edoxaban 60 mg: HR: 0.79 (0.63-0.99), $p < 0.0001$). However, in the edoxaban 30 mg (15 mg DA) group, results were not favorable for ischemic stroke [HR (95% CI): 1.54 (1.25-1.9), nominal $p < 0.0001$] and disabling stroke [HR (95% CI): 1.36 (0.91-2.03). For this reason, you are seeking approval to market only the 60 mg dose (30 mg DA) of edoxaban; we concur with this choice.

     As we have discussed with you previously, our central review issue continues to be inadequate efficacy in the subgroup of subjects with normal renal function (CrCL≥ 80 mL/min). For these subjects, the HR for first stroke/SEE for edoxaban 60 mg (30 mg DA) compared to warfarin group was 1.41 (95% CI: 0.97-2.05). The nominal p values for subgroup interaction were highly statistically significant (< 0.001 for the 60 mg dose and < 0.01 for the 30 mg dose). Less favorable results for the primary endpoint, its components, and CV death were consistently observed across edoxaban dose groups in subjects with CrCL≥80 mL/min.

     Our analysis indicates that the observed poorer outcomes relative to warfarin are closely correlated with lower edoxaban trough concentrations ($C_{troughs}$) in patients with normal renal function and so we believe the reduced concentrations are determinative. This conclusion is also supported by the observation that the most favorable reduction in stroke rate compared to warfarin [HR (95%CI): 0.53 (0.40 – 0.70)] was observed in patients with mild renal dysfunction (CrCL ≥50 – < 80 mL/min), the sub-group with highest edoxaban exposure in ENGAGE AF. Also, supportive is the observation that bleeding rates (relative to warfarin) were lower in edoxaban patients with normal renal function [HR (95%CI): 0.71 (0.55 – 0.90)] as compared to that in patients with mild renal dysfunction [HR (95%CI): 0.90 (0.75 – 1.08)].

     A formal exposure–response analysis using a multivariate Cox Proportional Hazards model identified edoxaban trough concentration, among others, as a significant predictor of efficacy

and safety. Similar relationships have been quantified for other thrombotic and safety events of interest including ischemic strokes, hemorrhagic strokes, life-threatening/fatal bleed, and major gastrointestinal bleed. In general, these relationships project a decrease in efficacy event rates with increasing edoxaban doses and a subsequent increase in safety event rates with increasing edoxaban doses. Projected relative risk estimates for the primary efficacy and safety endpoints by doses corresponding to exposure within the current clinical trial experience (< 95th percentile of observed $C_{troughs}$ in ENGAGE AF) is presented in the table below. A similar approach could also be applied to patients with moderate impairment of renal function (CrCL ≥30 – <50 mL/min) to further reduce the risk of stroke/SEE while projecting the increase in bleeding risk.

Table Risk ratio based on stroke/SEE and major bleed event rates projected for edoxaban with doses greater than that studied in ENGAGE AF. Risk ratios are presented relative to the observed event rate for warfarin and grouped by renal function category.

Endpoint	Renal Function Category	Comparison[#]	Risk Ratio
Stroke/SEE	Normal (CrCL≥ 80mL/min)	Edoxaban 60 vs Warfarin*	1.41
		Edoxaban 75 vs Warfarin	1.12
		Edoxaban 90 vs Warfarin	1.05
	Moderately Impaired (CrCL ≥30 – <50 mL/min)	Edoxaban 30 vs Warfarin*	0.88
		Edoxaban 37.5 vs Warfarin	0.74
		Edoxaban 45 vs Warfarin	0.71
Major Bleed	Normal (CrCL≥ 80mL/min)	Edoxaban 60 vs Warfarin*	0.71
		Edoxaban 75 vs Warfarin	0.91
		Edoxaban 90 vs Warfarin	1.19
	Moderately Impaired (CrCL ≥30 – <50 mL/min)	Edoxaban 30 vs Warfarin*	0.75
		Edoxaban 37.5 vs Warfarin	0.79
		Edoxaban 45 vs Warfarin	1.10

*Observed Hazard Ratio
[#]Edoxaban dose listed for patients with moderate impairment of renal function denotes the dose administered after taking into account decreased renal function (i.e., subjects with moderate impairment of renal function are administered 50% of the overall treatment dose).

You have indicated that you believe that the discrepancy in observed outcomes among subjects with differing levels of renal function may be because of better outcomes in warfarin subjects with normal renal function. While outcomes in the warfarin arm were better in the normal renal function subgroup compared to outcomes in subjects with renal impairment, we believe that finding irrelevant. Similar results were observed for warfarin in this subgroup in trials of other NOACs. Comparisons of outcomes between subjects randomized to edoxaban and warfarin are more useful than nonrandomized comparison of results within warfarin subjects.

2. We are unlikely to support adjusting dose based on based on (b) (4)

(b) (4)

3. Co-administration of rifampin results in ~ 40% loss of total systemic edoxaban exposure (AUC). While an increase in systemic exposure to its equipotent active metabolite D21-2393 makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (C_{max}) to D21-2393. At trough (end of inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined. Loss in exposure is considered detrimental based on the identified exposure-response efficacy relationships and difference in response rates between the two edoxaban treatment arms (30 mg QD versus 60 mg QD). Hence, we are likely to recommend that edoxaban should not be co-administered with a P-gp inducer.

4. Patients with moderately impaired hepatic function (Child-Pugh B) may have intrinsic coagulation abnormalities. Hence we do not believe the results of exposure-response analysis in patients without hepatic impairment should be extrapolated to determine a dose in patients with hepatic impairment. Labels for previously approved Factor Xa inhibitors do not make a dosing recommendation for patients with moderately impaired hepatic function.

5. Dosing recommendations and labeling pertaining to intrinsic and extrinsic factors may differ between the indications being sought because of differences in the Phase 3 programs. To illustrate, the anti-arrhythmic drug dronedarone was prohibited in Hokusai VTE while required an edoxaban dose reduction in ENGAGE-AF. Different dosing recommendations may be necessary in this instance.

- ***Clinical – Atrial Fibrillation (ORIG-1)***

1. Our major concern is that analysis of exposure and outcomes in subjects with normal renal function suggests that lower exposures in this subgroup resulted in an unacceptable reduction in efficacy. We note that there is no unmet medical need because two other drugs proven superior to warfarin are approved for the same indication. Edoxaban offers no obvious advantage over those drugs and at the dose studied in ENGAGE AF appears to offer less protection against stroke in patients with normal renal function. Hence we believe that our concern about the efficacy of edoxaban in patients with normal renal function represents a serious impediment to approvability for patients with normal renal function, and possibly all patients. We have concerns about recommending a dose higher than that studied in ENGAGE-AF for patients with normal renal function based solely on an analysis of exposure and outcomes in ENGAGE-AF patients with mildly impaired renal function. Understanding the clinical effects of an increased dose may require an additional trial.

   Additionally, we are concerned that extrapolating bleeding outcomes solely on the basis of systemic edoxaban exposures may underestimate bleeding risk. If local gastrointestinal (GI) exposure affects the risk of GI bleeding, then the risk of GI bleeding consequent to administering a dose of edoxaban higher than studied in ENGAGE-AF will be higher than suggested by modeling based solely on systemic exposure. It may be necessary to perform a clinical trial to assess the risk of bleeding associated with an edoxaban dose greater than 60 mg daily.

2. The following information may need to be included in the label:

(1) Administration of edoxaban results in small changes in creatinine clearance and serum creatinine

(2) A description of the imbalance in interstitial lung disease (ILD) between the groups.. Our review of your recent submitted information with regard to ILD is still ongoing.

- ***Biostatistics – Atrial Fibrillation (ORIG-1)***

  There are no substantive review issues at this time.

- ***Clinical & Biostatistics – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)*** (b) (4)

  (b) (4)

ADVISORY COMMITTEE MEETING – ***Atrial Fibrillation (ORIG-1)***

Date of AC meeting: October 30, 2014
Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: October 9, 2014

Potential questions and discussion topics for AC Meeting are as follows:

1. DISCUSSION: Please comment on your interpretation of the primary endpoint, ischemic stroke, and bleeding results in the various subgroups based on renal function in the ENGAGE AF trial:

   a) Do you believe the observed differences in the effects of treatment among the renal function subgroups should be attributed to the play of chance?

   b) If not, do you believe the differences in outcomes should be attributed to differences in exposure to edoxaban among the subgroups?

   c) If there is uncertainty in your assessment, how uncertain are you and why?

   d) Do you believe that the observed discrepancies in outcomes among subgroups based on renal function in the ENGAGE AF trial are an important consideration in the approvability of edoxaban to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation?

2. DISCUSSION: Is it appropriate to consider recommending a dose for patients with well-preserved renal function or moderate renal impairment based on analysis of the relationship

between serum concentration of edoxaban and major efficacy and safety outcomes in ENGAGE-AF subjects with mild renal impairment?

Note: While recommending unstudied doses in labeling to account for factors that change exposure (e.g., renal impairment and drug-drug interactions) is routine, exposure matching would result in a recommending a dose in labeling higher than any dose studied in Phase 2 or Phase 3 studies of edoxaban.

3. DISCUSSION: Is it appropriate to consider approving edoxaban with labeling that discourages use in those with well-preserved renal function if one were not convinced that an appropriate dose for this patient subgroup had been determined?

   Note: Patients with well-preserved renal function constitute a minority of patients with non-valvular atrial fibrillation who are candidates for anticoagulation according to the ACC/AHA/ESC 2006 Guidelines. However, such labeling would be unprecedented.

4. VOTE: Approval of edoxaban for the reduction of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. In considering options a, b and c, you should assume that edoxaban will be approved for patients with moderately impaired renal function with a recommended dose lower than 60 mg.

   a) Edoxaban should be approved with a 60 mg dose recommended in the label for patients with well-preserved or mildly impaired renal function.
   b) Edoxaban should be approved, but a higher dose than 60 mg should be recommended in the label for patients with well-preserved renal function.
   c) Edoxaban should be approved, but only for patients with mild and moderate renal impairment.
   d) Edoxaban should not be approved at this time.

5. DISCUSSION: If edoxaban is approved, should the applicant perform additional studies to support dosing instructions? Please offer advice about the goals, control groups, and primary endpoints of such studies.

6. DISCUSSION: If edoxaban is not approved, what additional studies should the applicant perform to support approval? Please offer advice about the goals, control groups, and primary endpoints of such studies.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location: http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

- ***Atrial Fibrillation (ORIG-1)***

  Edoxaban is currently under review for the proposed indication of the reduction in the risk of stroke and system embolism in patients with nonvalvular atrial fibrillation (AF). The Division of Risk Management (DRISK) review team for this indication cannot make final determinations about the need for a Risk Evaluation and Mitigation Strategy (REMS) for edoxaban until the risk-benefit profile is further discussed at the October 30, 2014 meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC). Following AC discussions, including the committee's recommendations about the safety and efficacy profile of edoxaban, DRISK will make a recommendation on risk management strategies for the product.

- ***Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)*** (b) (4)

  No issues that would require a REMS for the VTE indication have been identified to date.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

- **Pharmacology & Toxicology**

  Some information of nonclinical studies was not included or not correctly interpreted in the labeling. We suggest following changes for sections 8.1, 8.2, 8.4, 12.1, 13.1, and 13.2 - (a) delete (b) (4) since there is not enough data to support; (b) use AUC to make exposure comparison between humans and animals whenever animal AUC is available; (c) include information about delayed avoidance response (a learning test) in female offspring (rats), lower body weight in juvenile rats, high mortality and liver findings in 2-year rat study; (d) provide separate information for males and females in the carcinogenesis section. Suggestions for labeling are here –

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SAVAYSA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Embryo-fetal development studies were conducted in pregnant rats and rabbits during the period of organogenesis. In rats, no teratogenic effects were seen when edoxaban was administered orally at doses up to 300 mg/kg/day, or 49-times the human dose of 60 mg/day (b) (4) body surface area (b) (4). Increased post-implantation loss occurred at 300 mg/kg/day, but this effect may be secondary to the maternal vaginal hemorrhage seen at this dose. In rabbits, no teratogenic effects were seen at doses up to 600 mg/kg/day (49-times the human exposure at a dose of 60 mg/day when based on AUC). Embryo-fetal toxicities occurred at maternally toxic doses, and included absent or small fetal gallbladder at 600 mg/kg/day, and increased post-implantation loss, increased spontaneous abortion, and decreased live fetuses and fetal weight at doses equal to or greater than 200 mg/kg/day, which is equal to or greater than 20-times the human exposure.

In a rat pre- and post-natal developmental study, edoxaban was administered orally during the period of organogenesis and through lactation day 20 at doses up to 30 mg/kg/day, which is up to 3-times the human exposure when based on AUC. Vaginal bleeding in pregnant rats and delayed avoidance response (a learning test) in female offspring were seen at 30 mg/kg/day.

8.2 Labor and Delivery

Safety and effectiveness of SAVAYSA during labor and delivery have not been studied in clinical trials. The risks of bleeding should be balanced with the risk of thrombotic events when considering the use of SAVAYSA in this setting.

(b) (4)

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established (b) (4)

12.1. Mechanism of Action

Edoxaban is a (b) (4) elective (b) (4) inhibitor of (b) (4) FXa, (b) (4) (b) (4) It does not require antithrombin III for antithrombotic activity. Edoxaban inhibits free FXa, and prothrombinase activity and (b) (4) inhibits thrombin-induced platelet aggregation. Inhibition of FXa in the coagulation cascade reduces thrombin generation (b) (4) and reduces (b) (4) (b) (4) thrombus formation.

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13. Nonclinical Toxicology

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Edoxaban was not carcinogenic when administered daily to mice and rats by oral gavage for up to 104 weeks. The highest dose tested (500 mg/kg/day) in male and female mice was 3 and 6 times, respectively, the human exposure (AUC) at the human dose of 60 mg/day, and the highest doses tested in male (600/400 mg/kg/day) and female (200 mg/kg/day) rats were 8 and (b) (4) times, respectively, the human exposure at the human dose of 60 mg/day.

Edoxaban and its human-specific metabolite, M-4, were genotoxic in *in vitro* chromosomal aberration tests but were not genotoxic in the in vitro bacterial reverse mutation (Ames test), in *in vitro* human lymphocytes micronucleus test, in in vivo rat bone marrow micronucleus test, *in vivo* rat liver micronucleus test, and in in vivo unscheduled DNA synthesis tests.

Edoxaban showed no effects on fertility and early embryonic development in rats at doses of up to 1000 mg/kg/day (162 times the human dose of 60 mg/day (b) (4) body surface area).

(b) (4)

- ***Clinical & Biostatistics – Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)*** (b) (4)

1. You seek the full approval of Edoxaban for the indications: treatment of DVT and PE (b) (4) We find support for treatment of DVT and PE (b) (4)

2. (b) (4)

3. (b) (4)

4. (b) (4)

5. In Figure 14.3 in the labeling. (b) (4) makes the figure confusing to read. The figure should be revised to show cumulative incidence rate for recurrent VTE or VTE-related death based on mITT population for overall study period only.

6. (b) (4)

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **October 13, 2014**. The resubmitted labeling will be used for further labeling discussions. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms to format items in regulations and guidances.

LCM AGENDA

1. Introductory Comments – 5 minutes (Alison Blaus – RPM & Martin Rose - CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 30 minutes

   Each issue will be introduced by FDA and followed by a discussion.

3. Outstanding Information Requests – 5 minutes

4. Discussion of Upcoming Advisory Committee Meeting – 25 minutes

5. REMS or Other Risk Management Actions – 5 minutes

6. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

   - PMR- DHP for PREA
   - PMC for dissolution

7. Major labeling issues – 10 minutes

8. Review Plans – 5 minutes

9. Wrap-up and Action Items – 5 minutes

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

/s/

NORMAN L STOCKBRIDGE
09/29/2014

ANN T FARRELL
09/29/2014