

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204886Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Department of Health and Human Services Food and Drug Administration  <b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>	NDA NUMBER 204886
	NAME OF APPLICANT / NDA HOLDER Merck Sharp & Dohme Corp.

**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) TRADEMARK
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ACTIVE INGREDIENT(S) Vorapaxar sulfate	STRENGTH(S) 2.5 mg
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DOSAGE FORM Tablets, oral
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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 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 file 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 US 7,235,567 B2	b. Issue Date of Patent June 26, 2007	c. Expiration Date of Patent June 13, 2021
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d. Name of Patent Owner Merck Sharp & Dohme Corp.	Address (of Patent Owner) Office of General Counsel One Merck Drive-WS3B-70A, P.O. Box 100	
	City/State Whitehouse Station, New Jersey	
	ZIP Code 08889	FAX Number (if available) (908) 735-1247
	Telephone Number (908) 423-3761	E-Mail Address (if available) paul.matukaitis@merck.com

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.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
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g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
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**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.

Applicant understands question 2.2 to ask whether the patent claims only a different polymorph than that described in the pending NDA and answered "no" on that basis. The patent claims the form of the active ingredient described in the NDA and is submitted for listing on that basis.

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? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	--

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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4. Method of Use (continued)	
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific 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



March 15, 2013

**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

Mark W. Russell

Address

Merck, P.O. Box 2000, RY-86-2111A

City/State

Rahway, New Jersey

ZIP Code

07065

Telephone Number

(732) 594-0469

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

mark.russell@merck.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

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*

NDA NUMBER  
204886

NAME OF APPLICANT / NDA HOLDER  
Merck Sharp & Dohme Corp.

*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)  
TRADEMARK

ACTIVE INGREDIENT(S)  
Vorapaxar sulfate

STRENGTH(S)  
2.5 mg

DOSAGE FORM  
Tablets, oral

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 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 file 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  
US 7,304,078 B2

b. Issue Date of Patent  
December 4, 2007

c. Expiration Date of Patent  
April 6, 2024

d. Name of Patent Owner  
  
Merck Sharp & Dohme Corp.

Address (of Patent Owner)  
Office of General Counsel  
One Merck Drive-WS3B-70A, P.O. Box 100

City/State  
Whitehouse Station, New Jersey

ZIP Code  
08889

FAX Number (if available)  
(908) 735-1247

Telephone Number  
(908) 423-3761

E-Mail Address (if available)  
paul.matukaitis@merck.com

e. Name of agent or representative who resides or main-tains a place of business within the United States author-ized 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.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

**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.

Questions 2.2, 2.3 and 2.4

The claims of United States Patent No. 7,304,078 B2 are not limited to any particular polymorphic form of the drug substance. The patent claims encompass all polymorphic forms of the drug substance described in the pending, amendment or supplement NDA reference above to the extent that they exist. Because the patent is submitted for listing on that basis, no testing of other polymorphic forms of the drug substance is required, and Questions 2.2, 2.3 and 2.4 are accordingly left blank.

- 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) 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 31, 33, 34, 36, 38, 39, 41, 43, 44, 46, 48, 49, 51, 53, 54, 56, 58, and 59
- 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 specific reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

Use: Reduction of atherothrombotic events in patients with a history of myocardial infarction in accordance with the approved labeling, including the Indications and Usage, Dosage and Administration, and Clinical Pharmacology sections.

4. Method of Use (continued)	
4.2 Patent Claim Number(s) (as listed in the patent) 61, 62, 63, 64, 65, 66 and 67	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? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Use: Treatment of atherothrombotic events through inhibition of thrombin induced platelet aggregation in a patient in accordance with the approved labeling, including the Indications and Usage, Dosage and Administration, and Clinical Pharmacology sections.
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with specific 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



March 15, 2013

**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

Mark W. Russell

Address

Merck, P.O. Box 2000, RY-86-2111A

City/State

Rahway, New Jersey

ZIP Code

07065

Telephone Number

(732) 594-0469

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

mark.russell@merck.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 204886

SUPPL # n/a

HFD # 110

Trade Name: ZONTIVITY

Generic Name: vorapaxar

Applicant Name: Merck, Sharpe, & Dohme

Approval Date: 9 May 2014

### 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?

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).

NDA# n/a

NDA# n/a

NDA# 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).

NDA# n/a

NDA# n/a

NDA# 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.)  
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 8:

(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

If yes, explain:

(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

If yes, explain:

- (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.")

Investigation #1 YES  NO

Investigation #2 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?

Investigation #1 YES  NO

Investigation #2 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?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # 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?

Investigation #1  
!  
! YES  NO   
! Explain: ! Explain:

Investigation #2  
!  
! YES  NO   
! Explain: ! 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: Alison Blaus, RAC  
Title: Regulatory Health Project Manager  
Date: 28 April 2014

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

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

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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.**  
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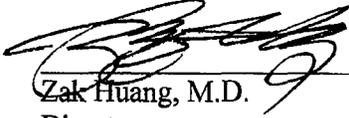
/s/  
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ALISON L BLAUS  
04/28/2014

NORMAN L STOCKBRIDGE  
04/28/2014

Vorapaxar Sulfate (MK-5348 / SCH 530348): Original Marketing Application  
Debarment Certification

The applicant cited on the Form FDA 356h included with this submission 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.



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Zak Huang, M.D.  
Director  
Worldwide Regulatory Affairs

*April 22, 2013*

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Date

## ACTION PACKAGE CHECKLIST

<b>APPLICATION INFORMATION<sup>1</sup></b>		
NDA # 204886 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: ZONTIVITY Established/Proper Name: vorapaxar Dosage Form: 2.08 mg Tablets		Applicant: Merck, Sharpe, & Dohme Agent for Applicant (if applicable): n/a
RPM: Alison Blaus, RAC		Division: Cardiovascular & Renal Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p style="margin-left: 20px;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: _____         </p> <p><i>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.</i></p>	
❖ <b>Actions</b>		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>10 May 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, (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 <sup>3</sup>	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NME ( <i>confirm chemical classification at time of approval</i> )  <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request  BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies  REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required  Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: FDA Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes
• If so, specify the type	Five Year NCE

<sup>3</sup> 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.

❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action and date: Approval 8May14
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 27Jun13 DMEPA: <input type="checkbox"/> None 14Feb14 & 28Mar14 DMPP/PLT (DRISK): <input type="checkbox"/> None 19Feb14 OPDP: <input type="checkbox"/> None 1May14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None Patient Labeling – 2May14

<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting) (indicate date of each review)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee</li> </ul>	RPM Filing Review: 24Jun14 RPM Overview: 12May14  <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (signed by Division Director)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> <ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> <li>• This application is on the AIP                             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (approvals only)                             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC 20Nov13</li> <li>If PeRC review not necessary, explain: <u>n/a</u></li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (do not include previous action letters, as these are located elsewhere in package)</li> </ul>	Included
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	Included
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings                             <ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (indicate date of mtg)</li> <li>• Pre-NDA/BLA meeting (Topline on 25Apr12 and Pre-NDA on 19Jun12 )</li> <li>• EOP2 meeting (27Feb07)</li> <li>• Mid-cycle Communication (31Oct13)</li> <li>• Late-cycle Meeting (3Jan14)</li> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg  <input type="checkbox"/> No mtg Topline minutes dated 21May12; Pre-NDA minutes dated 2Jul12  <input type="checkbox"/> No mtg minutes dated 16Mar07  <input type="checkbox"/> N/A minutes dated 4Dec13  <input type="checkbox"/> N/A minutes dated 31Jan14  CMC Meeting on 9Jan14
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting                             <ul style="list-style-type: none"> <li>• Date of Meeting: 15Jan14</li> </ul> </li> </ul>	<input type="checkbox"/> No AC meeting  Quick Minutes Included
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (indicate date for each review)</li> </ul>	<input type="checkbox"/> None 8May14
<ul style="list-style-type: none"> <li>Division Director Summary Review (indicate date for each review)</li> </ul>	<input type="checkbox"/> None 25Apr14
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review (indicate date for each review)</li> </ul>	<input type="checkbox"/> None 18Apr14
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates (indicate total number)</li> </ul>	<input checked="" type="checkbox"/> None

<sup>4</sup> Filing reviews for scientific disciplines should be filed with the respective discipline.

<b>Clinical</b>	
❖ <b>Clinical Reviews</b>	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	<b>Primary Clinical Reviews:</b> 17Jun13 (Filing Review); 16Dec13 (Primary Review); 18Apr14 (Addendum) <b>Ophthalmology Reviews</b> dated 29Oct13 & 5May14
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	16Apr14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>• REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul>	10 May 2013 n/a <input type="checkbox"/> None 19Feb14
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input type="checkbox"/> None requested 20Mar14
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7Jun13
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 17Jun13 (Filing Review); 13Dec13 (Primary Review); 20Dec13 (Addendum)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 17Jun13 (Filing Review); 16Dec13 (Primary Review)
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested 29Apr14

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 6May14
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12Jun13 (Filing Review); 17Dec13 (Primary Review); 19Feb14 (Addendum)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None 29Oct13 (Ophthalmology)
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc 21Oct13
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 16Oct13 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 29Jan14
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 14Jun13 (Initial Quality Assessment); 14Jun13 (Filing Review); 9Jan14 (Primary Review)
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 7Jun13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None 9Jan14 (Biopharmaceutics Review)
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See Quality Primary Review dated 9Jan14
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 5Sep13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<sup>5</sup> 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.

❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)
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<b>Day of Approval Activities</b>	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> 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.**  
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/s/  
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ALISON L BLAUS  
05/09/2014



NDA 204886

**GENERAL ADVICE**

Merck Sharp & Dohme Corp.  
Attention: Jeffrey Tucker, M.D., Executive Director  
Worldwide Regulatory Affairs  
One Merck Drive  
P.O. Box 100  
Whitehouse Station, NJ 08889

Dear Dr. Tucker:

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

We also refer to your February 12, 2014, submission, containing samples of the labels, labeling, and packaging (carton & container) for the 5 tablet sample blister pack with the carton and the unit dose blisters with the carton.

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

Ensure that the established name is at least ½ the size of the proprietary name on all labels and labeling, taking into account all pertinent factors including typography, layout, contrast and other printing features as per 21 CFR 201.10(g)(2).

If you have any questions, please call:

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

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular & 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.**  
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/s/  
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NORMAN L STOCKBRIDGE  
02/25/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 204886

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dome Corp.  
126 East Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065-0900

ATTENTION: Chitkala Kalidas, Ph.D.  
Director, Worldwide Regulatory Affairs

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated and received May 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vorapaxar Tablets, 2.08 mg.

We also refer to:

- Your correspondence, dated May 15, 2013, received May 16, 2013, requesting review of your proposed proprietary name, Zontivity
- Our August 9, 2013, Proprietary Name Request Conditionally Acceptable letter to Merck Sharp & Dome Corp.
- Your NDA amendment, dated and received December 20, 2013, containing revision to the expression of the strength of the Vorapaxar tablet
- Our December 30, 2013, email correspondence requesting that the proposed proprietary name be resubmitted for review
- Your correspondence, dated and received January 3, 2014, requesting review of your proposed proprietary name, Zontivity

We have completed our review of the proposed proprietary name, Zontivity, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 3, 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 Office of New Drugs, at (301) 796-1138.

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/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
01/31/2014

**From:** [Kalidas, Chitkala](#)  
**To:** [Bengtson, Karen](#)  
**Cc:** [Blaus, Alison](#)  
**Subject:** RE: VORAPAXAR NDA (NDA 204886): RESPONSE TO DMEPA  
**Date:** Monday, December 30, 2013 11:58:11 AM  
**Importance:** High

---

Dear Ms. Bengtson-

Thanks for your message. I will submit the requested updated information to you as soon as possible. In the meantime, I just wanted to mention that besides the revised strength, an additional statement has been included in the product labeling.

The product strength was revised from 2.5mg to 2.08 mg at the request of the ONDQA and a statement that “**Each tablet contains 2.08mg vorapaxar, equivalent to 2.5mg vorapaxar sulfate**” was included in the product labeling.

Best regards,  
Chitkala

---

**From:** Bengtson, Karen [mailto:[Karen.Bengtson@fda.hhs.gov](mailto:Karen.Bengtson@fda.hhs.gov)]  
**Sent:** Monday, December 30, 2013 9:48 AM  
**To:** Kalidas, Chitkala  
**Cc:** Blaus, Alison  
**Subject:** RE: VORAPAXAR NDA (NDA 204886): RESPONSE TO DMEPA  
**Importance:** High

Dear Dr. Kalidas,

Given the revision in the strength product characteristic (i.e., from 2.5 mg to 2.08 mg) for NDA 204886, the proprietary name will need to be resubmitted for review as stated in the “Proprietary Name Request Conditionally Acceptable” letter dated August 9, 2013. Please resubmit with the updated information as soon as possible.

Kind regards,  
Karen

Karen Bengtson | Safety Regulatory Project Manager | Office of Surveillance and Epidemiology | CDER | FDA  
10903 New Hampshire Avenue, WO Bldg.22, Room 4483 | Silver Spring, MD 20993  
☎ 301.796.3338 (phone) ✉ [Karen.Bengtson@fda.hhs.gov](mailto:Karen.Bengtson@fda.hhs.gov)

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**From:** Kalidas, Chitkala [[mailto:chitkala\\_kalidas@merck.com](mailto:chitkala_kalidas@merck.com)]  
**Sent:** Monday, December 23, 2013 1:28 PM  
**To:** Childers, Alexis  
**Cc:** Blaus, Alison  
**Subject:** VORAPAXAR NDA (NDA 204886): RESPONSE TO DMEPA  
**Importance:** High

Dear Ms. Childers-

I am sending this message to you in Alison Blaus' absence with a request to forward it to DMEPA. Attached are the packaging labels that Merck is providing in response to the request from DMEPA (included in the message below) to provide physical samples.

I had informed Ms. Blaus earlier that we are unable to provide the physical samples at this time as they are not available. However, we hope that the copies of the packaging labels showing the exact location of the cavities in the blister packs along with other labeling components (with and without the template view) will help the DMEPA Reviewers assess the readability of the packaging labels.

Please let me know if you have any questions. The attached documents will be submitted via the e-gateway today. I am sending this to you as a courtesy copy for DMEPA. Thanks in advance for sending this to the OSE-DMEPA Reviewer.

Best regards,  
Chitkala

**Chitkala Kalidas, Ph.D.**  
Director  
Global Regulatory Affairs  
Phone: 732-594-0599

**h**

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**From:** Blaus, Alison [<mailto:Alison.Blaus@fda.hhs.gov>]  
**Sent:** Friday, December 13, 2013 8:40 AM  
**To:** Kalidas, Chitkala  
**Subject:** NDA 204866 - Mockups

Good morning –

The OSE-DMEPA reviewer is currently reviewing your labeling and they would like you to please submit samples of the labels, labeling, and packaging (carton-container) for the following:

- The 5 tablet sample blister pack with the carton

- The unit dose blisters with the carton

Given our review timeline for DMEPA, we request a response no later than **COB Tuesday, December 17, 2013**.

Please confirm receipt of this request via email.

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](mailto: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/  
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KAREN E BENGTON  
01/23/2014

**Summary Minutes of the Drug Safety and Risk Management Advisory Committee Meeting**

**January 15, 2014**

**Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center**

**(Rm. 1503), Silver Spring, MD**

**All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.**

**These summary minutes for the January 15, 2014 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on March 11, 2014.**

**I certify that I attended the January 15, 2014 Meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.**

\_\_\_\_\_/s/\_\_\_\_\_  
**Kristina A. Toliver, PharmD**  
**Designated Federal Officer**  
**Cardiovascular and Renal Drugs**  
**Advisory Committee**

\_\_\_\_\_/s/\_\_\_\_\_  
**Philip Sager, MD**  
**Chairperson**

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 15, 2014 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Room 1503), Silver Spring, Maryland, 20993. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and [REDACTED] (b) (4). The meeting was called to order by Philip Sager, MD (Acting Chairperson); the conflict of interest statement was read into the record by Kristina A. Toliver, PharmD (Designated Federal Officer). There were approximately 125 people in attendance. There were no Open Public Hearing speakers.

**Issue:** The committee discussed New Drug Application 204886, vorapaxar tablets, submitted by Merck Sharp & Dohme Corp. for the proposed indication of reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). The applicant also proposes that vorapaxar has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

**Attendance:**

**Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):**

Scott Emerson, MD, PhD; Linda F. Fried, MD, MPH; Julia B. Lewis, MD; Jennifer S. Li, MD, MHS; Stuart Rich, MD; Philip Sager, MD (Acting Chairperson)

**Cardiovascular and Renal Drugs Advisory Committee Members (Non-Voting):**

Rob Scott, MD (Industry Representative)

**Cardiovascular and Renal Drugs Advisory Committee Members Not Present:**

James DeLemos, MD; A. Michael Lincoff, MD (Chairperson); Vasilios Papademetriou, MD

**Temporary Members (Voting):**

Robert Dubbs (Patient Representative); Richard P. Hoffmann, PharmD (Acting Consumer Representative); Sanjay Kaul, MD; Mori J. Krantz, MD; Michael Proschan, PhD, MS

**FDA Participants (Non-Voting):**

Norman Stockbridge, MD, PhD; Robert Temple, MD; Ellis Unger, MD

**Designated Federal Officer (Non-Voting):**

Kristina A. Toliver, PharmD

**Open Public Hearing Speakers:** None

***The agenda proceeded as follows:***

Call to Order and Introduction of  
Committee

**Philip Sager, MD**  
Acting Chairperson, CRDAC

Conflict of Interest Statement

**Kristina A. Toliver, PharmD**  
Designated Federal Officer, CRDAC

FDA Introductory Remarks

**Norman Stockbridge, MD**  
Director  
Division of Cardiovascular and Renal Products (DCaRP)  
Office of Drug Evaluation I (ODEI)  
Office of New Drugs (OND), CDER, FDA

**SPONSOR PRESENTATIONS**

**Merck Sharp & Dohme Corp.**

Introduction to Vorapaxar

**Chitkala Kalidas, PhD**  
Director, Merck Regulatory Affairs

Clinical Program Overview



Vorapaxar Pivotal TRA 2°P – TIMI 50  
Results in the Overall Population

**David Morrow, MD, MPH**  
Senior Investigator, TIMI Study Group  
Brigham and Women's Hospital

TRA 2°P – TIMI 50 Results in  
Proposed Label Population

**Daniel Bloomfield, MD**  
Vice President, Clinical Research  
Merck Research Laboratories

Vorapaxar Benefit-Risk

**Eugene Braunwald, MD**  
Founding Chairman, TIMI Study Group  
Brigham and Women's Hospital

Clarifying Questions

**BREAK**

**FDA PRESENTATIONS**

Clinical & Statistical Issues

**Martin Rose, MD, JD**  
Clinical Reviewer  
DCaRP, ODEI, OND, CDER, FDA

Clarifying Questions

**LUNCH**

Open Public Hearing

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

***Questions to the Committee:***

The Advisory Committee is asked to opine on the approvability of vorapaxar, an antagonist of protease-activated receptor-1 (PAR-1), for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI).

The support for this claim comes primarily from TRA2°P, a randomized, double-blind, placebo-controlled trial of vorapaxar 2.5 mg once daily in addition to standard therapy including other antiplatelet agents. The TRA2°P study population consisted of 26,449 subjects with prior MI, prior ischemic stroke (in either case, the event occurred from 2 weeks to 12 months prior to study entry), or established peripheral arterial disease (PAD).

Vorapaxar was also tested in TRACER, a randomized, double-blind, placebo-controlled trial of vorapaxar 2.5 mg daily after a 40-mg loading dose, also in addition to standard therapy including other antiplatelet agents. The TRACER study population consisted of 12,944 patients who had acute coronary syndromes (ACS) without ST-segment elevation within 24 hours before hospital presentation. TRACER was terminated early because of an increased rate of major bleeding, including intracranial hemorrhage (ICH), in the vorapaxar arm.

Subjects with a history of stroke were also terminated early in TRA2°P. TRA2°P was completed in the remainder of the population and the reported results show efficacy for vorapaxar. For the primary endpoint of cardiovascular (CV) death, MI, or stroke, the hazard ratio was 0.87 (95% confidence interval [CI] 0.80-0.94,  $p < 0.001$ ). There was a higher rate of ICH in the vorapaxar group (1.0% vs. 0.6%,  $p < 0.001$ ).

- I. Comment on the evolution of the protocol for TRA2°P and its impact on study interpretation.
  - a. TRACER and TRA2°P shared one Data Safety Monitoring Board. Does this present any problems with their interpretation? **DISCUSSION**
  - b. TRA2°P was planned to have one interim analysis when 50% of the primary and key secondary events had been observed. What was the plan for how this interim analysis could impact the study? Was there any problem with that? **DISCUSSION**

**Committee Discussion:** Questions 1-a and 1-b were discussed together. The committee stated that it would have been ideal to have separate data safety monitoring boards (DSMBs) to limit the potential for cross contamination; however, the methodologies that were used were reasonable and there's no significant impact on interpretability of the study from having a single DSMB versus two DSMBs. With regard to the interim analysis, the committee stated that it was planned and the other two safety analyses do not significantly impact the study. Please see the transcript for details of the committee discussion.

- c. How many interim analyses were actually conducted for TRA2°P? How do these impact its interpretation? **DISCUSSION**

**Committee Discussion:** The committee stated that there was one formal analysis and two safety analyses. It was noted that the interim analyses did not impact the study in a meaningful manner. Please see the transcript for details of the committee discussion.

2. Comment on the evolving sample size in TRA2°P.

- a. TRA2°P began with a plan to observe 2279 primary end point events and 1322 key secondary events. At some point, the study was resized to ensure 1400 key secondary events. Why was that? What is the impact of this on study interpretation? **DISCUSSION**

**Committee Discussion:** The committee stated that the resizing of the study was done in a reasonable manner and that the resizing didn't impact study interpretation in a meaningful manner. Please see the transcript for details of the committee discussion.

- b. TRA2°P had 2676 primary end point events and 2204 key secondary events. Why are these so much larger than the planned sizes? What impact does this have on study interpretation? **DISCUSSION**

**Committee Discussion:** The committee stated that the overrun was secondary to the amount of time it took to close out the study, and that a greater number of events were accrued during that time period than what was anticipated. It was noted that the overrun had a direct impact on the interpretation of the study. Please see the transcript for details of the committee discussion.

3. Comment on adequacy of follow-up in TRA2°P.

- a. How does the loss to follow-up impact your interpretation of these results?  
**DISCUSSION**

**Committee Discussion:** The committee stated that the small loss to follow-up didn't impact the overall interpretation of the study results. Please see the transcript for details of the committee discussion.

- b. In what respects was this similar to other cardiovascular development programs?

**DISCUSSION**

*Committee Discussion:* The committee stated that compared to other recent outcome studies in the cardiovascular arena, this follow-up was really good. Please see the transcript for details of the committee discussion.

4. Overall study results are as follows:

	Incidence (%)		
	Placebo	Vorapaxar	Vor-Pla
Any 1° endpoint event	10.7	9.5	-1.2
All-cause death	4.3	4.1	-0.2
CV Death	2.4	2.2	-0.2
MI	5.1	4.3	-0.8
Stroke	2.5	2.4	-0.1
Ischemic	2.1	1.8	-0.3
...Hemorrhagic	0.2	0.6	0.4
Uncertain	0.1	0.2	0.1
Urgent coronary revasc	2.4	2.1	-0.3

Subjects may have had more than one of these events.

Is the benefit/risk evaluation favorable for vorapaxar in the overall population of TRA2°P?

**DISCUSSION**

*Committee Discussion:* The committee stated that the benefit/risk profile was determined to be positive. There was a call for more granularity regarding what some of these events may mean to patients when they are non-mortal events. The committee also stated that MIs and strokes come in a wide range and that it would be nice, albeit complicated, to look at these events as a spectrum with more than just a binary way of evaluating the events. Please see the transcript for details of the committee discussion.

5. The applicant seeks approval in a subpopulation of the TRA2°P trial, i.e., only in patients with a history of MI and no history of stroke or TIA.

- a. Do you agree with the sponsor's proposed restriction regarding history of *stroke*? If so, should this be for any history of stroke or within some period? **DISCUSSION**

*Committee Discussion:* The committee members stated that they agreed with the sponsor's restriction regarding history of stroke. It was stated that patients with any history at all of stroke should be restricted from using vorapaxar. Please see the transcript for details of the committee discussion.

- b. Do you agree with the sponsor's proposed restriction regarding history of *TIA*? If so, should this be for any history of TIA or within some period? **DISCUSSION**

*Committee Discussion:* The committee members stated that they agreed with the sponsor's restriction regarding history of TIA. It was stated that patients with any

*history at all of TIA should be restricted from using vorapaxar. Please see the transcript for details of the committee discussion.*

6. The review team finds that a restriction on weight achieves similar risks and benefits in subjects regardless of history of stroke or TIA. Is this more plausible or less reasonable a restriction? **DISCUSSION**

**Committee Discussion:** *The committee stated that more data is needed to understand and examine the benefit/risk ratio in patients weighing less than 60 kg. They stated that data regarding the finding in patients less than 60 kg should be in section 14 (Clinical Studies) of the label. It was also stated that there should be language in section 5 (Warnings and Precautions) that patients weighing less than 60 kg may have an increased risk of bleeding and that the overall benefit/risk ratio in these patients should be considered. Please see the transcript for details of the committee discussion.*

7. What should labeling say about use of vorapaxar with antiplatelet agents other than clopidogrel plus aspirin? **DISCUSSION**

**Committee Discussion:** *The committee stated that the label should remain silent about the use of vorapaxar with antiplatelet agents other than clopidogrel plus aspirin or the label should say that it hasn't been studied. Please see the transcript for details of the committee discussion.*

- a. Please give additional guidance regarding labeling, including the use of vorapaxar in peripheral artery disease. **DISCUSSION**

**Committee Discussion:** *The committee stated that, in terms of labeling, it didn't make sense in the context of the study to carve out another subgroup where there was not a safety issue. It was also stated that if the drug is approved, it is important that the labeling focus on the population studied in terms of the post-MI, which patients its use is restricted in, and those type of caveats. Please see the transcript for details of the committee discussion.*

8. Should vorapaxar be approved? If so, for whom? **VOTE**

**Yes: 10            No: 1            Abstain: 0**

**Committee Discussion:** *The majority of the committee members agreed that vorapaxar should be approved. The committee members who voted "Yes" stated that TRA2°P was a large and robust study and the benefit/risk ratio was favorable. It was stated that vorapaxar meets an unmet medical need and the effect size of the study makes it clinically meaningful. However, these members also expressed concern about the risks of bleeding and the lack of an antidote. They also called for continued surveillance of adverse events in patients weighing less than 60 kg. The committee member who voted "No" expressed concern about the size of the benefit in endpoints that were harder (specifically intracranial hemorrhage), and about the amplification of the signal because of the unprecedented use of triple antiplatelet therapy. Please see the transcript for details of the committee discussion.*

9. Vorapaxar, like other antiplatelet and anticoagulant agents, presents a tradeoff between efficacy (reduced atherothrombotic events) and safety (increased bleeding).
- a. What is the best way to evaluate this tradeoff? **DISCUSSION**
    - i. Subjectively assess separate analyses of safety and efficacy?
    - ii. Net clinical benefit analyses?
    - iii. A formal, weighted composite safety and efficacy endpoint?

***Committee Discussion:** The committee stated that in the future, development of weighted, composite, quantitative assessments of safety and efficacy could add value but one needs to look at the totality of the data of this subjective analyses or important net clinical benefit. Some committee members were less positive about that approach, but other committee members thought it also added value. Please see the transcript for details of the committee discussion.*

- b. Can you rank order the events under consideration – CV death, MI, ischemic or hemorrhagic stroke, or urgent revascularization – or do you need information on the consequences of these events? **DISCUSSION**

***Committee Discussion:** The committee stated that it is difficult to rank order the events under consideration (CV death, MI, ischemic or hemorrhagic stroke, or urgent revascularization) because it is important to consider what the individual consequences of the events are and that how large the impact is on the patient should be considered. When ranked by the committee, urgent revascularization was on the low end of rank order and CV death was often at the top. However, it was noted that major central nervous system events can supersede CV death when considering patient consequences. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at 4:40 p.m.

# MEMORANDUM OF TELECON

DATE: January 9, 2014

APPLICATION NUMBER: NDA 204886

BETWEEN:

**Merck Sharp & Dohme Corp. :**

List of Attendees:

## **CMC**

Dr. Ganapathy Mohan, Executive Director  
Dr. Jeffrey Ding, Director  
Dr. Steve Liang, Director  
Ms. Tracy Gaebele, Associate Director  
Ms. Brooke Marshall, Senior Specialist

## **Project Leadership**

Dr. James Zega, Director

## **Regulatory Affairs**

Dr. Jeffrey Tucker, Executive Director  
Dr. Chitkala Kalidas, Director

AND

**Office of New Drug Quality Assessment:**

List of Attendees:

Dr. Minerva Hughes, Acting Biopharmaceutics Lead  
Dr. Okpo Eradiri, Biopharmaceutics Reviewer  
Dr. Thomas Wong, Product Quality Reviewer  
Yvonne Knight, Regulatory Health Project Manager

SUBJECT: Dissolution Acceptance Criterion

Background:

On January 2, 2014, the Agency contacted Merck Sharp & Dome Corp. requesting a tele-conference to discuss Merck's responses to the most recent Biopharmaceutics Information Request Letter. The teleconference was to focus on the Applicant's justification for the updated proposed dissolution acceptance criterion of Q = (b) (4)

The Call:

On January 9, 2014, the Agency informed Merck that for predicted failure the 25/60 data was best for long term stability condition. The Agency then stated the Q= $\text{[REDACTED]}^{(b)(4)}$  was not the best time point and that Q= $\text{[REDACTED]}^{(b)(4)}$  at 30 min. is the best and appropriate time point for this product.

After deliberation Merck agreed to the new acceptance criterion and provided an email confirmation of the acceptance criterion (see email attachment). The sponsor also agreed to submit the revised CTD section of 3.2.P.5.1 Specifications to the NDA by Jan 14, 2014. Merck conveyed they would like to evaluate the dissolution specification after approval with additional commercial production experience and seek the Agency's guidance at the time if necessary.

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Regulatory Health Project Manager

**From:** [Kalidas, Chitkala](#)  
**To:** [Knight, Yvonne](#)  
**Subject:** VORAPAXAR (NDA 204886): ACCEPTANCE OF DISSOLUTION CRITERIA  
**Date:** Thursday, January 09, 2014 2:21:16 PM  
**Importance:** High

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Dear Ms. Knight-

Thank you for the opportunity to discuss the dissolution acceptance criteria this morning. Based on the discussion, we accept the Agency's recommendation of Q=<sup>(b) (4)</sup> at 30 minutes for the dissolution acceptance criteria. We would like to evaluate the dissolution specification after approval with additional commercial production experience and seek the Agency's guidance at the time if necessary.

We will submit the revised CTD section of 3.2.P.5.1 Specifications to the NDA by Jan 14, 2014.

Best regards,  
Chitkala

**Chitkala Kalidas, Ph.D.**  
Director  
Global Regulatory Affairs  
Phone: 732-594-0599

**h**

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/s/  
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YVONNE L KNIGHT  
01/09/2014



NDA 204886

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Chitkala Kalidas., Director  
Worldwide Regulatory Affairs  
126 E. Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Kalidas:

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

We also refer to your May 10, 2013, 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 December 31, 2013, in order to continue our evaluation of your NDA.

Product Quality

Your response dated Nov 18 to our comment on the expression of the strength of the tablet is not acceptable. You should follow the MAPP 5021 and USP <1121> nomenclature for naming the tablet strength. The strength of the tablets should be expressed as our recommendation sent to you on Oct 4 which is:

Trademark (Vorapaxar) Tablets 2.08 mg\*

\*Equivalent to 2.5 mg vorapaxar sulfate

Due to the conversion of some of the sulfate salt to the free base at the time of manufacture and upon storage, we recommend you to add a statement to the Description (Section 11) of the Package Insert such as "Brand Name tablets are formulated with vorapaxar sulfate, but during manufacture and storage, partial conversion from vorapaxar sulfate to vorapaxar free base may occur".

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/  
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OLEN M STEPHENS  
12/06/2013



NDA 204886

**MID-CYCLE COMMUNICATION**

Merck Sharp & Dohme Corp.  
Attention: Chitkala Kalidas, Ph.D.  
Director, Worldwide Regulatory Affairs  
126 E. Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

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

We also refer to the teleconference between representatives of your firm and the FDA on 31 October 2013. 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:

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

Sincerely,

*{See appended electronic signature page}*

Thomas Marciniak, M.D.  
Clinical Team Leader  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** 31 October 2013 from 930 to 1100 EST  
**Application Number:** NDA 204958  
**Product Name:** vorapaxar sulfate  
**Proposed Indication:** **Patients with History of Myocardial Infarction (MI)**  
ZONTIVITY (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).  
**Applicant Name:** Merck Sharp & Dohme Corp.  
**Meeting Chair:** Thomas Marciniak, M.D.  
**Meeting Recorder:** Alison Blaus, RAC

**FDA ATTENDEES**

*\* Office of Drug Evaluation 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
Martin Rose, M.D., JD	Clinical Reviewer
Jonathan Levine, Ph.D.	Clinical Reviewer
Thomas Papoian, Ph.D.	Team Leader, Pharmacology/Toxicology
Patricia Harlow, Ph.D.	Pharmacology/Toxicology Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Health Project Manager

*\* Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D.	Team Leader
Sudharshan Hariharan, Ph.D.	Reviewer

*\* Office of Biostatistics*

Yeh-Fong Chen, Ph.D.	Statistician
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*\* Office of New Drug Quality Assessment*

Kasturi Srinivasachar, Ph.D.	Branch Chief
Thomas Wong, Ph.D.	Reviewer
Okpo Eradiri, Ph.D.	Biopharmaceutics

*\* Office of Surveillance and Epidemiology*

Reema Mehta, PharmD	DRISK Team Leader
Jamie Wilkins-Parker, PharmD	DRISK Reviewer
Danielle Smith, PharmD	DRISK Reviewer

*\* Office of Planning and Analysis*

Kimberly Taylor	Operations Research Analyst
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### **EASTERN RESEARCH GROUP ATTENDEES**

Christopher Sese Independent Assessor

### **APPLICANT ATTENDEES**

#### **\* Clinical Research**

Barry Gertz	Senior Vice President, Clinical Research
Daniel Bloomfield	Vice President, Clinical Research
John Strony	Executive Director, Clinical Research
Gil Gleim	Director, Clinical Research
Leslie Lipka	Director, Clinical Research
Chris Morabito	Associate Director, Clinical Research
Meredith Murray	Associate Principal Scientist, Clinical Research
Christi Kent	Senior Scientist, Clinical Research

#### **\* Regulatory**

Scott Korn	Vice President, Regulatory Affairs
Jeff Tucker	Executive Director, Regulatory, Affairs
Chitkala Kalidas	Director, Regulatory Affairs
Lina AlJuburi	Director, Regulatory Policy

#### **\* Statistics**

Bruce Binkowitz	Executive Director, Biostatistics
Weili He	Director, Biostatistics
Yabing Mai	Associate Principal Scientist, Biostatistics
Adam Polis	Director, Biostatistics
Rob Hoffman	Scientific Programmer – Accenture

#### **\* Clinical Pharmacology**

Matt Anderson	Director, Clinical Pharmacology
David Gutstein	Executive Director, Clinical Pharmacology

#### **\* Drug Metabolism and Pharmacometrics**

Thomas Kerbusch	Executive Director, Pharmacometrics
Marissa Dockendorf	Principal Scientist, Quantitative Sciences
Mark Wirth	Senior Principal Scientist, Pharmacokinetics
Ferdous Gheyas	Senior Principal Scientist, Pharmacometrics
Rebecca Wrishko	Senior Principal Scientist, Quantitative Sciences

#### **\* Pre-clinical**

John Petrulis	Director, Toxicology
Dietmar Seiffert	Executive Director, Biology-Discovery

#### **\* Risk Management**

Jenny Yu	Executive Director, Drug Safety
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#### **\* Chemistry, Manufacturing, & Controls**

Jeffrey Ding	Director, Regulatory Affairs
James Zega	Director, CMC Project Management

#### **\* Epidemiology**

Cathy Anne Pinto	Associate Principal Scientist, Epidemiology
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#### **\* Project Leadership**

Gail Murphy	Executive Director, Project Leadership
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## 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

- Dr. Wong conveyed to the applicant that they were currently reviewing the free base formation and the specified control strategy and analytical methods. The sponsor asked for the Division's rationale for the thirty minute dissolution acceptance criterion of (b)(4). Dr. Eradiri explained that they reviewed the raw stability data and that (b)(4) and 30 minutes was too permissive and should be tightened. The applicant acknowledged the Agency's rationale.

### Pharmacology & Toxicology

- Dr. Harlow noted that at this time she did not have an approvability issues, but did have some labeling comments to convey. She explained that based on her review of the reproductive & toxicology study, she will suggest the inclusion of pre/post-natal development results in labeling. She noted that in her opinion the cross-fostering study did not negate the pre-post natal development study as the applicant suggested.

### Clinical Pharmacology

- Dr. Hariharan explained that clinical pharmacology is contemplating how to label the discontinuation of vorapaxar prior to CABG since the time to completely offset the pharmacodynamic effect is >4 weeks. He said that he will be working with Dr. Rose to look at the clinical experience during TRACER to inform labeling.
- Information Request - Dr. Hariharan asked the sponsor to provide information on the use or discontinuation of thienopyridines and aspirin prior to CABG (i.e., one or both discontinued, how far ahead of CABG, etc.).

### Clinical

- Data Awaiting Review
  - Dr. Rose said that there were a few areas of the application that still warranted review. He explained that he will be reviewing the interaction with age and weight and also will be reviewing liver laboratory data from TRACER and TRAP-2P.
  - Information Request – Dr. Rose explained that more review of drug interactions was needed. He was specifically interested in those drugs that decreased exposure. Dr. Rose requested that the sponsor reproduce the drug interaction analyses they did for 7 days but for 30 days. The

sponsor can examine the same drugs, but those of specific interest were H2 blockers, Proton-pump Inhibitors (PPIs), and CYP3A inducers.

- Labeling
  - Dr. Rose explained that the post-hoc decision to limit the indication to the Applicant's proposed label population may have implications for Section 14 (Clinical Studies) and Section 6 (Adverse Reactions). For example, the information from TRACER regarding the the rate of ICH in vorapaxar arm subjects without a history of stroke is of concern. Dr. Rose went on to explain that the current proposed indication was selected post-hoc and may or may not be representative of true magnitude of the effects of vorapaxar on efficacy and safety endpoints. .
  - Information Request – Dr. Rose would like the applicant's thoughts on the labeling implications of the post-hoc choice of the indication.
  
- Cancer
  - Dr. Marciniak said that he had still to review the relationship of vorapaxar and solid cancers. He added that he will review the data before the advisory committee, and will specifically review the rates and how the patients were followed-up.

#### **Biostatistics**

- Dr. Chen said that during the course of TRAP-2P, there were a number of unplanned interim analyses and some sample size re-estimation that appear to be conducted through the DMC in an unblinded manner . The DMC reviewed not only safety data, but also efficacy, which raises potential trial integrity concerns. Dr. Chen noted that this will be a topic for the 15 January 2014 Advisory Committee although the DMC does not need to be present for that presentation and subsequent discussion.

### **3.0 INFORMATION REQUESTS**

At the time of the Mid-cycle Communication Meeting, there were a number of outstanding information requests. An abridged list of all outstanding information requests are as follows:

- ALL data from the Visit Status CRF page
- Description of randomization of subjects and a justification for why they were not always sequential
- CMC Information Request Letter (dated 4 October 2013)
- EDISH Datasets
- Cause of death analysis
- Risk vs. Benefit analysis (for TRACER and TRAP - 2P) - as discussed at the 16Oct13 informal teleconference
- Letters to the sites and/or investigators from TRACER
- New TRAP-2P Clinical Study Report Figures 19 and 22 - From first dose to last dose plus 30 days. Provided for treated patients and for the "proposed label" population

For the information requested at the mid-cycle communication meeting, please see Section 2.0, Significant Issues, where these requests are highlighted.

#### 4.0 MAJOR SAFETY CONCERNS & RISK MANAGEMENT

##### Safety Concerns

- Please see the discussion under the section “Significant Issues – Clinical” section. The significant concerns that were raised at the meeting overlap with safety concerns.

##### Risk Management Plan (REMS)

- It was noted by Jamie Wilkins Parker of DRISK that at this time no safety issues have been identified that rise to the level of a REMS, but that they will continue to follow-up with Clinical Safety Reviewer/Team throughout their review. The sponsor is encouraged to disseminate their communications materials outside of a REMS.

#### 5.0 ADVISORY COMMITTEE MEETING

As mentioned in our 22 July 2013 Day 74 Letter, we are planning on holding an advisory committee (AC) to discuss this application. Some helpful advisory committee meeting dates are as follows:

**Advisory Committee Meeting Book Due (Merck): 11 December 2013**  
**Advisory Committee Meeting Book Due (FDA): 16 December 2013**  
**FDA Slides Due: 13 January 2014**  
**AC: 15 January 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): 19 December 2013**  
**Late Cycle Meeting Briefing Book Due to Medicines Company: 25 December 2013**  
**Late-Cycle Meeting w/Sponsor: 3 January 2014**

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/s/  
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ALISON L BLAUS  
12/04/2013

THOMAS A MARCINIAK  
12/04/2013

**PeRC PREA Subcommittee Meeting Minutes  
November 20, 2013**

**PeRC Members Attending:**

Lynne Yao  
Rosemary Addy  
Hari Cheryl Sachs  
George Greeley  
Jane Inglese  
Wiley Chambers  
Tom Smith  
Karen Davis-Bruno  
Colleen LoCicero  
Gregory Reaman  
Daiva Shetty  
Shrikant Pagay  
Ruthanna Davi  
Kevin Krudys  
Lily Mulugeta  
Maura O'Leary  
Robert Nelson  
Dianne Murphy  
William J. Rodriguez

**Agenda**

10:55

11:10

(b) (4)

NDA 204886 Zonitivity (vorapaxar) Full Waiver

(b) (4)

**Zonitivity (vorapaxar) Full Waiver**

- NDA 204886 seeks marketing approval for Zonitivity (vorapaxar) for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI).
- The application has a PDUFA goal date of May 10, 2014.
- The application triggers PREA as directed to a new active ingredient.
- *PeRC Recommendations:*
  - The PeRC agreed with a full waiver because studies are impossible or highly impractical because the disease/condition does not occur in children.

(b) (4)

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/s/  
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JANE E INGLESE  
12/02/2013

## **Executive CAC**

**Date of Meeting: October 15, 2013**

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair  
Abigail Jacobs, Ph.D., OND -IO, Member  
Paul Brown, Ph.D., OND-IO, Member  
Aisar Atrakchi Ph.D., DPP, Alternate Member  
Thomas Papoian, Ph.D., DCRP, Supervisor  
Patricia Harlow, Ph.D., DCRP, Presenting Reviewer

Author of Draft: Patricia Harlow, Ph.D.

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

**NDA: 204-886**

**Drug Name: Vorapaxar (SCH 530848)**

**Sponsor: Merck (Schering Plough)**

### **Background:**

Vorapaxar is an inhibitor of the protease activated receptor 1 (PAR-1), also known as the thrombin receptor. In the Phase 3 trial for reduction of atherothrombotic events in patients with a history of myocardial infarction, the daily vorapaxar dose was 2.5 mg.

### **Rat Carcinogenicity Study:**

Sprague Dawley rats (50/sex/group) received daily oral doses of 0, 3, 10, and 30 mg/kg/day of vorapaxar administered by oral gavage in 0.4% (w/v) aqueous methylcellulose for 105-106 weeks. As specified in the Exec CAC's concurrence of the protocol, the male and female rats were fed 21 gm and 17 gm, respectively, of food per day, as was done in the 3-month and 6-month dose-ranging studies. The total exposures to vorapaxar in the high dose males and females were 10 and 28 fold, respectively, the mean total exposure in patients receiving the recommended human dose (RHD) of 2.5 mg.

No significant treatment-related effects were observed on mortality, and food consumption. However, the mean body weight gain decreased up to 16% and 17% in the high dose males and females, respectively, compared to the control groups.

The high dose females had increased incidences of uterine adenoma and the high dose males had increased incidences of basal cell tumor of the skin and histiocytic sarcoma. However, the p values for these tumors did not attain the significance level required for the neoplasms to be considered drug related.

Although the high dose female rats had an increased incidence of hepatocellular adenoma that was 4-fold above the maximum of the sponsor's historical control range (0-2%), the p values for both the trend test and the pairwise test for this tumor did not attain the criteria ( $p_t < 0.005$  and  $p_p < 0.01$ ) required for a common tumor to be considered positive. It

should be noted that the incidence of hepatocellular adenoma in the concurrent control group was 1%, the lower threshold for being considered a common tumor ( $\geq 1\%$ ).

**Mouse Carcinogenicity Study:**

CD-1 mice (50/sex/group) received daily oral doses of 0, 1, 5, and 15 mg/kg/day of vorapaxar administered by oral gavage in 0.4% (w/v) aqueous methylcellulose for 103 to 104 weeks. The total exposures to vorapaxar in the high dose males and females were 28 and 34 fold, respectively, the mean total exposure to vorapaxar in patients receiving the RHD of 2.5 mg. A metabolite of vorapaxar, SCH 2046273, represents about 25% of the vorapaxar plasma concentration in humans. The exposures to SCH 2046273 in the high dose males and females were 5.5 and 6.3-fold the mean exposure to SCH 2046273 in patients receiving the RHD of 2.5 mg.

No significant treatment-related effects were observed on mortality or food consumption. However, the high dose male and female groups gained 16% and 14%, respectively, less bodyweight than the control group.

The incidence of bronchiolo-alveolar adenoma increased in the high dose females and the incidence of bronchiolo-alveolar carcinoma increased in the high dose males. However, the p values for each of these tumors and their combination in the trend test did not attain the significance level of  $p < 0.005$  required for these common tumors to be considered positive.

**Executive CAC Recommendations and Conclusions:**

Rat:

The Committee considered that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no drug-related neoplasms in male or female rats.

Mouse:

The Committee considered that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no drug-related neoplasms in male or female mice.

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

cc:\

/Division File, DCRP  
/T. Papoian, Supervisor, DCRP  
/P. Harlow, Reviewer, DCRP  
/A. Blaus, CSO/PM, DCRP  
/A.Seifried, OND-IO

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/s/  
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ADELE S SEIFRIED  
10/16/2013

DAVID JACOBSON KRAM  
10/16/2013



NDA 204886

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Zak Huang, M.D., Director  
Worldwide Regulatory Affairs  
351 North Summeytown Pike UG2CD-48  
P.O. Box 1000  
North Wales, PA 19454

Dear Dr. Huang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vorapaxar Sulfate Tablets, 2.5 mg.

We also refer to your May 10, 2013, 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.

Product Quality

1. Include a test for [REDACTED] (b) (4) with appropriate acceptance criteria in the specifications of the vorapaxar free base.
2. In the drug substance specification, include a test with acceptance criteria for heavy metals per USP<231>.
3. Regarding your formulation development studies on the impact of excipients on free base formation, provide the levels of free base [REDACTED] (b) (4).
4. In Section P.3.3 - Detailed Description for the Method of Manufacture:
  - a [REDACTED] (b) (4) in the Process Parameter Controls table.
  - b Include the process parameters [REDACTED] (b) (4) in the Process Parameter Controls table.
  - c Include the hold time limits as described in P.2.3 - Manufacturing Process Development, Table 57 for the intermediates [REDACTED] (b) (4).

Labeling

5. Revise the labeling to read as: Trademark (Vorapaxar) Tablets 2.08 mg\*  
\*Equivalent to 2.5 mg vorapaxar sulfate.

Biopharmaceutics

6. In the investigation of the discriminating power of your proposed dissolution method, results of your factorial design experiments were not compared to the target formulation to identify parameters which alter the release profile significantly to necessitate batch rejection. Perform the  $f_2$  similarity and/or other appropriate test for each formulation relative to the target and then draw conclusions on the discriminating power of the method. Provide these data
7. In the excipient level change experimental formulations, the free base content is within a narrow range (b) (4) whereas the (b) (4) parameter formulations show a wider array of free base (b) (4). Please clarify if the free base levels in Tables 4 and 5 in your response (Response 2 Attachment) were (b) (4)
8. The proposed dissolution acceptance criterion of  $Q =$  (b) (4) is not supported by the data and is therefore not acceptable. The dissolution data support a criterion of  $Q =$  (b) (4) % at 30 min. Implement this acceptance criterion for the dissolution test and provide an updated specification Table for the dug product.

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/  
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OLEN M STEPHENS  
10/04/2013



NDA 204886

**METHODS VALIDATION  
MATERIALS RECEIVED**

Merck Sharp & Dohme  
Attention: Zak Huang, MD, Worldwide Regulatory Affairs  
P.O. Box 1000  
North Wales, PA 19454-2505  
FAX: (267) 305-6406

Dear Dr. Huang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zontivity (vorapaxar sulfate), tablets, 2.5 mg and to our July 11, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 9, 2013, 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

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/s/  
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MICHAEL L TREHY  
08/20/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 204886

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merck Sharp and Dohme Corp.  
351 North Sumneytown Pike  
P.O. Box 1000, UG2CD-48  
North Wales, PA 19454

ATTENTION: Zak Huang, M.D.  
Director, Worldwide Regulatory Affairs

Dear Dr. Huang:

Please refer to your New Drug Application (NDA), dated and received May 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vorapaxar Sulfate Tablets, 2.5 mg.

We also refer to your correspondence dated May 15, 2013, received May 16, 2013, requesting review of your proposed proprietary name, Zontivity. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Zontivity, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 16, 2013 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 Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Alison Blaus at 301-796-1138.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
08/09/2013



NDA 204886

**FILING COMMUNICATION**

Merck Sharp & Dohme Corp.  
Attention: Chitkala Kalidas, Ph.D.  
Director, Worldwide Regulatory Affairs  
126 E. Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated May 10, 2013, received May 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for vorapaxar sulfate.

We also refer to your amendments dated May 15, 16, 20, 23, and 30 (two), June 4, 6, 7 (two), 11 (four), 18, 20, and 21, and July 9, 2013.

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 **May 10, 2014**.

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 **January 27, 2014**. In addition, the planned date for our internal mid-cycle review meeting is **October 24, 2013**. We are 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:

1. In January 2011, a series of changes in the conduct of the TRA2P-TIMI 50 trial were made in response to a recommendation of the DSMB to discontinue study drug in subjects with a history

of stroke and to continue the trial as planned in other subjects. The DSMB's recommendation was based on an extensive unblinded and unscheduled interim review of the study data. We have the following questions regarding these study conduct changes:

- a. Your study report and other NDA documents do not discuss whether the changes in the study that occurred in January 2011 had any effect on study alpha error. Please address this issue, and quantify the change in alpha error. If you believe there was no effect on alpha error, explain your rationale.
  - b. Please provide operational details regarding how subjects with a prior stroke were notified to discontinue drug. We note that many subjects had their final study visit at this time. How long after discontinuation of study drug did the final visit occur for these subjects?
  - c. In CSR Tables 8 through 10, you describe the follow-up to be performed in various subgroups of subjects with prior stroke who had discontinuation of treatment in January 2011. We note that some such subjects were to have their final study visit (and presumably their final study contact) at that time, while others to be contacted at the end of the study. Provide a rationale for your decisions regarding follow-up, focusing on why you decided to terminate follow-up on some subjects but not others. We note that subjects in the vorapaxar arm with a prior stroke had an increased risk of intracranial hemorrhage (ICH) compared to analogous subjects in the placebo arm. You should address the issue of potential bias introduced by early discontinuation of follow-up.
2. On June 20, 2013 you provided us with information regarding subjects who had early discontinuation of follow-up followed by subsequent ascertainment of vital status. It is our understanding that such patients were censored for the primary endpoint on the date of the ascertainment of vital status, even though their last contact providing information about non-fatal stroke and MI occurred at an earlier date. You should re-run your primary endpoint analysis with censoring of these patients on the last date when information on all components of the primary endpoint was available.
  3. According to your DSMB meeting minutes for TRA2P-TIMI 50 trial, we noted that 11 interim analyses were conducted, where only one of them was pre-planned to analyze the efficacy results in an unblinded manner. Although the p-values for the primary endpoints were not reported in the minutes for the remaining 10 unplanned interim analyses, the event rates of the treatment groups were observed. Please explain why these efficacy analyses were conducted and exactly what analyses had been performed for each interim analysis. Similar to Issue #1, please explain how these unblinded efficacy analyses would affect the study alpha level.

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.

We request that you submit the following information:

1. From the structure of vorapaxar, the salt should be [REDACTED] (b) (4). Originally, this substance was called [REDACTED] (b) (4) but later in development the name was changed to vorapaxar sulfate. Provide rationale for this change in nomenclature.
2. **Dissolution Test:** Please submit the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

- a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. We recommend use of at least twelve samples per testing variable;
  - b. Justify the choice of equipment, dissolution medium and rotation speed;
  - c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);
  - d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm 10\text{-}20\%$  change to the specification-ranges of these variables). If available, provide data showing the capability of the proposed dissolution method and acceptance criterion to reject batches that are not bioequivalent.
3. **Dissolution Acceptance Criterion:** Provide the following data/information regarding the setting of dissolution acceptance criterion for your product:
- a. Tabulated individual vessel dissolution data for the pivotal clinical batches and primary (registration) stability batches used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value). Provide descriptive statistics at all sampling time points.
  - b. You have predicted dissolution testing failure rates as justification of the proposed acceptance criterion. The use of accelerated stability data in predicting failure rates at the 45 and 60 minute time points is not acceptable. Please repeat the computations using room temperature stability data and submit the results to the NDA.
4. **Bridging of the To-be-marketed (TBM) tablets to the Clinical Trial tablets (CTM):** Provide the individual vessel dissolution data, along with descriptive statistics, that bridge the proposed TBM product to the CTM. If the raw data permit, compute and report the f2 profile comparison.
5. All of the toxicology studies were conducted with vorapaxar free base, whereas the clinical trials were conducted with vorapaxar sulfate. Please justify why a toxicology or bridging study was not conducted with vorapaxar sulfate.
6. Please justify the specifications for the (b) (4) degradants in the drug product given that these impurities were not found in any lot of vorapaxar used in a toxicology study. Please confirm, either by an Ames test or by QSAR analysis, that (b) (4) degradants are not genotoxic.
7. Please clarify what potentially genotoxic impurities are present in the drug substance even if they are controlled to be present at levels less than the Toxicological Threshold of Concern (TTC) of  $1.5 \mu\text{g}/\text{day}$ .
8. Please provide the following items for both TRA CER and TRA 2P-TIMI 50 trials :
- a. Please provide the detailed algorithm for capturing patient-level data analyzed in the interim analysis from your submitted data sets.
  - b. Please provide detailed interim analysis results including the event rates and hazard ratio in comparing study drug with placebo for the primary endpoint and also for each component endpoint. Please also provide the same type of analysis results for the patients who had history of strokes and those who did not have history of strokes.
  - c. For each component of the primary endpoint, please provide analysis results for time to each component event using the same method for the primary endpoint.

9. For TRA 2P-TIMI 50 trial, we noted that about 7,000 additional patients were randomized and analyzed beyond the originally planned sample size. Please provide your explanation for why the sample size was increased.
10. We note that the “Administrative Head of Drug Safety Surveillance” was provided with the randomization schemes during the trial. What is the rationale for providing this person with these documents prior to data lock? How were these documents to be used during the trial?
11. How many subjects were unblinded in TRA 2<sup>P</sup> by the mechanism described on page 95 of the study report? How many persons were unblinded in TRACER by a similar mechanism? Did you confirm that in each case of such unblinding, the “study hotline had been consulted” as described in the study report and that the study physician agreed that unblinding was necessary?
12. It is unclear which numerical versions of the normal ranges in the laboratory datasets correspond to the lab values in original units (NUMRSLT) or SI units (ABSRSLT). At least one of the normal ranges appears to be missing, and after looking at the data it is unclear if the variables HI and LO represents the normal range for SI or original units. Please submit new datasets with numeric versions of the normal ranges both SI and original units for all laboratory datasets.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Please center the title of the Boxed Warning in the **HIGHLIGHTS**.
2. In the **INDICATIONS AN USAGE** section the established name or the route should not be noted, therefore, please change  
  
"TRADEMARK (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1) is indicated.."  
  
To  
  
""TRADEMARK is an antagonist of the protease-activated receptor-1 (PAR-1) indicated..".
3. “**WARNING: BLEEDING RISK**” is missing from the Table of Contents (TOC), between “Full Prescribing Information” and Section 1. Please add.
4. In section 6.1, **Clinical Trials Experience**, the standard statement, “Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.” should be used verbatim and should precede the presentation of adverse reactions not follow them.
5. Per 21 CFR 201.57, since there are no studies in the pediatric patient population, subsection 8.4 should contain only the below verbatim statement:  
  
“Safety and effectiveness in pediatric patients have not been established”

We request that you resubmit labeling that addresses these issues by **August 13, 2013**. The resubmitted labeling will be used for further labeling discussions.

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, 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), 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. 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

If you have any questions, please call:

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

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ALISON L BLAUS  
07/22/2013

NORMAN L STOCKBRIDGE  
07/22/2013



NDA 204886

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Merck Sharpe & Dohme  
Attention: Zak Huang, MD  
Worldwide Regulatory Affairs  
351 North Sumneytown Pike  
UG2CD-48  
P.O.Box 1000  
North Wales, PA 19454-2505  
FAX: (267) 305-6406

Dear Zak Huang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zontivity (vorapaxar sulfate), tablets, 2.5 mg.

We will be performing methods validation studies on Zontivity (vorapaxar sulfate), tablets, 2.5 mg, as described in NDA 204886.

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

**Method, current version**

Drug Substance:

Analytical Procedures – Assay and Degradation Products by HPLC  
Particle Size by Laser Diffraction

Drug Product:

Analytical Procedures – Assay and Degradation Products by HPLC  
Vorapaxar Free Base by FT Raman

**Samples and Reference Standards**

- 2 x 1 g reference standard, vorapaxar sulfate
- 100 mg of vorapaxar free base if available
- 100 mg of vorapaxar sulfate salt if available
- 5 g drug substance, vorapaxar sulfate
- 10 bottles each containing 50 tablets/bottle 2.5 mg/tablet Lot No. K-H11413
- 0.5 g system suitability sample SCH 1375358 (b)(4) Lot No. L-004922135-000E002
- 20 mg SCH 1394451 (b)(4) if available
- 20 mg SCH 1513919 (b)(4) if available
- 20 mg SCH 789908 (b)(4) if available
- 20 mg SCH 789909 (b)(4) if available
- 20 mg SCH 1394446 (b)(4) if available
- 20 mg SCH 1375206 (b)(4) if available

**Equipment**

1 octadecylsilane 100 mm x 4.6 mm, (b) (4) size column.

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  
1114 Market Street, Room 1002  
St. Louis, MO 63101

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/  
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MICHAEL L TREHY  
07/11/2013



NDA 204886

**NDA ACKNOWLEDGMENT**

Merck Sharp & Dohme Corp.  
Attention: Zak Huang, M.D.  
Director, Worldwide Regulatory Affairs  
P.O. Box 1000, UG2CD-48  
North Wales, PA 19454

Dear Dr. Huang:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: MK-5348/SCH 530348 (vorapaxar sulfate) Tablets, 2.5 mg

Date of Application: May 10, 2013

Date of Receipt: May 10, 2013

Our Reference Number: NDA 204886

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 July 9, 2013, 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).

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 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 and Renal 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, please 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](mailto: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 contact:

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

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

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/s/  
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EDWARD J FROMM  
05/17/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 71384

**MEETING MINUTES**

Merck Sharp & Dohme Corp.  
Attention: Zak Huang, M.D.  
Director, Worldwide Regulatory Affairs  
P.O. Box 1000, UG2CD-48  
North Wales, PA 19454

Dear Dr. Huang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for vorapaxar (SCH 530348).

We also refer to the meeting between representatives of your firm and the FDA on 19 June 2012. The purpose of the meeting was to discuss the format and content of your planned dossier.

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

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., PhD  
Director  
Division of Cardiovascular & 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:** 19 June 2012 from 1300 – 1415 EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, Maryland 20903  
**Application Number:** IND 71384  
**Product Name:** vorapaxar (SCH 530348)  
**Original Proposed Indication:** Reduction of atherothrombotic events in patients with a history of myocardial infarction or peripheral arterial disease  
**Sponsor Name:** Merck Sharp & Dohme Corp.  
**Meeting Chair:** Norman Stockbridge, M.D., PhD  
**Meeting Recorder:** Alison Blaus

### FDA ATTENDEES

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

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Martin Rose, M.D.	Clinical Reviewer
Kathie Lillie, M.D.	Clinical Reviewer
Patricia Harlow, Ph.D.	Pharmacology/Toxicology
Edward Fromm, R.Ph., RAC	Chief, Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager

*\* Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D	Team Leader
Sudharshan Hariharan, Ph.D.	Reviewer
Michael Pacanowski, Ph.D.	Pharmacogenomics Reviewer
Hobart Rogers, Ph.D.	Pharmacogenomics Reviewer
Christopher Lee	Pharmacy Student

*\* Office of Biostatistics*

Yeh-Fong Chen, Ph.D.	Statistician
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### SPONSOR ATTENDEES

John Strony, M.D.	Section Head, Thrombosis
Francis Plat, M.D.	Vice President, Clinical Research
Leslie Lipka, PhD, M.D.	Director, Clinical Research
Edmond Chen, M.D.	Director, Clinical Research
Bruce Binkowitz, Ph.D.	Senior Director, Late Development Statistics
Weili He, Ph.D.	Director, Late Development Statistics
Gail Murphy, M.D.	Senior Project Leader, Cardiovascular
Mary Frances Schubert, M.D.	Senior Director, Clinical Risk Management
Ekopimo Okon Ibia, M.D., MPH	Director, US Regulatory Policy Lead
Teddy Kosoglou, Pharm D	Senior Director, Clinical Pharmacology
Paul Statkevich, Ph.D.	Director, Clinical PK/PD
Ferdous Gheyas, Ph.D.	Director, Modeling and Simulation

Scott Korn, M.D.  
Jeffrey Tucker, M.D.  
Zak Huang, M.D.

Vice President, Worldwide Regulatory Affairs  
Senior Director, Worldwide Regulatory Affairs  
Director, Worldwide Regulatory Affairs

## 1.0 BACKGROUND

Vorapaxar, or SCH 530348, is an antagonist of the protease-activated receptor-1 (PAR-1) that inhibits thrombin-induced platelet aggregation. At the End of Phase 2 meeting on 16 March 2007, the sponsor proposed two trials:

- **TRA-CER** - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome. Patients in this trial were either randomized to placebo or 40mg loading dose of vorapaxar followed by a daily maintenance dose of 2.5mg.
- **TRA 2P/TIMI 50** - a multinational, multicenter, double blind trial to evaluate the efficacy and safety of vorapaxar in addition to standard of care, compared to placebo in addition to standard of care in the secondary prevention of ischemic events in patients with established atherosclerotic disease, as manifested by coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial disease (PAD). The primary endpoint in this trial was the reduction in the incidence of cardiovascular death, myocardial infarction (MI), stroke and urgent coronary revascularization relative to standard of care alone. Patients in 2P were randomized to receive either 2.5 mg daily of vorapaxar or matching placebo.

TRACER was stopped for an unacceptably increased risk of intracranial hemorrhage in subjects taking vorapaxar. Based on those results, subjects in TIMI 50 with a previous history were immediately discontinued from study drug.

The sponsor previously met with the Agency on 25 April 2012 (minutes dated 21 May 2012) to present the results from both trials, TRACER and TIMI 50. This meeting was scheduled to discuss the format and content of their planned dossier, which includes the trial discussed in April.

## 2. DISCUSSION

### 2.1. Questions for the Agency

1. Does the Agency note any deficiencies in the planned nonclinical toxicology and safety pharmacology program (Table 1) to support the registration of vorapaxar for use as chronic antiplatelet therapy in patients with a history of myocardial infarction?

#### *FDA Preliminary Response*

No deficiency in the nonclinical toxicology and safety pharmacology program is currently apparent.

#### *Discussion at the Meeting*

No further discussion.

2. Does the Agency agree that the content and presentation of the clinical pharmacology program will be adequate to allow filing of the NDA in support of review and registration of vorapaxar?

**FDA Preliminary Response**

Yes. Attached to these responses is the Clinical Pharmacology Review Aid (Appendix I). Please refer to this document when putting together clinical pharmacology information in your dossier.

**Discussion at the Meeting**

The Agency requested the sponsor submit in their NDA a completed Clinical Pharmacology Review Aid (outline attached to the preliminary comments document), which is a standalone document with hyperlinks intended to speed the review. The sponsor noted that they may not have time to prepare such a document, but asked if they could instead place the requested information in Section 2.71 and 2.72. The Agency said that they would prefer the standalone document, but the alternative proposal would be acceptable.

3. Does the Agency agree with the Sponsor's approach for pharmacokinetic and pharmacokinetic / pharmacodynamic modeling and that this approach would aid the Agency in review of the NDA?

**FDA Preliminary Response**

Yes. We also recommend you to explore the possibility of utilizing these PK/PD models to simulate the PK and PD for TRA\*<sup>CER</sup> and TRA-2<sup>°P</sup> for understanding their relationship to efficacy/bleeding outcomes.

**Discussion at the Meeting**

Merçk explained that they did not collect PK data in TRA-2P and only had approximately 30 samples from TRACER. Dr. Madabushi acknowledged the sponsor's available data, but explained that his comment was about the sponsor using the PK/PD models developed based on Phase 2 study data. Using these models the sponsor could estimate steady state exposures for the doses studied in their Phase 3 trial to explore the relationship between the simulated exposure and efficacy/safety outcome data. Dr. Madabushi asked the sponsor to include this in the initial NDA submission.

4. Based on the Table of Contents for the CTD sections 2.5, 2.7.3, and 2.7.4, does the Agency agree that the planned organization and presentation of the efficacy and safety results from the vorapaxar clinical development program are adequate to support the filing and review of vorapaxar NDA to support an indication in patients with history of MI?

**FDA Preliminary Response**

Please include an Integrated Summary of Safety that contains the information specified in guidance document, Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (1988). Whether the application is adequate for filing is a review issue.

Section 2.7.4.2.2 Narratives, should include subheadings, preferably by study, then by each unique subject ID (hyperlinked). The thorough QT study (P03462) report should be hyperlinked in Section 2.7.4.4.2 ECG findings. Please include the reference to the IND and submission of the QT data on September 27, 2010 (serial 0668) when discussing the TQT data since you have no plans to submit these data to the NDA. The Summary of Clinical Safety should include a section that outlines what was done to stop the bleeding and an assessment of the success of the procedures used. Appendix 1 Regulatory history of interactions with FDA should include hyperlinks to FDA meeting minutes/response or comments.

**Discussion at the Meeting**

No further discussion.

5. Thus, the Sponsor proposes to provide the following: 1) Bleeding events, adverse events, laboratory values, vital signs, and ECGs from the TRA\*CER and TRA-2°P studies in the as-treated population (defined as subjects who were randomized and received at least one dose of study drug) are to be shown separately for each study, 2) Bleeding events will be summarized based on a pool of the TRA\*CER experience beyond the first 30 days post-randomization along with the overall TRA-2°P experience in the as-treated population, and 3) Adverse events, laboratory values, vital signs, and ECGs will be summarized based on a pool of the overall TRA\*CER and TRA-2°P experience in the as-treated population. Does the Agency concur?

**FDA Preliminary Response**

Yes. On a related note, please report and provide data to calculate the annual event rate for all events. We note that for some events you reported the 3 year event rate.

**Discussion at the Meeting**

The Division clarified that the above annualized event rate request was for both TRACER and TRA-2P.

6. Does the Agency concur that the format of the prototype Clinical Study Report is acceptable to support the filing and review of the NDA?

**FDA Preliminary Response**

In general, yes. Please include the following specific items in the report or elsewhere in the initial NDA submission at locations that are easily identified:

- Dates of first patient in, last patient visit, and database lock
- A general statement regarding compliance with GCP
- An analysis of adverse events leading to discontinuation, under a heading that describes the analysis
- Charters for all study committees
- Minutes of meetings of the DSMB and for of all groups with any responsibility for the conduct of your trial (such as executive committees), including minutes of closed sessions
- All materials and presentations (e.g., copies of slide sets) provided to the DSMB, groups with any responsibility for the conduct of your trial (such as executive committees), and the Steering Committee of national coordinators.
- All versions of monitoring plans, including all amendments, and all communications to the sites (either all sites or a subset of sites > 1 site) about changes in monitoring (Both TRA-2P and TRACER).
- A document describing triggers for adjudication, if not included in another document
- A SAS dataset with one line for each event sent for adjudication , that has the following fields
  - The endpoint being adjudicated and the date of the event
  - The trigger for adjudication

- The investigator's assessment of the event (if the investigator did not make an assessment, this should be derived based on the definition and information the investigator provided)
- Each adjudicator's result and date (these should be listed chronologically as one reads across the row).
- The final adjudication result
- The database should be structured so that the reviewer can easily find cases where the adjudication result did or did not agree with the investigator's determination
- The number of levels of adjudication required
- Adjudication ID number, if any
- Site and unique subject ID
- AE ID, if any
- Reason for not adjudicating the event, if not adjudicated
- Randomized treatment arm

#### **Discussion at the Meeting**

The Division clarified that the above requests were for both TRACER and TRA-2P. The sponsor asked whether the request, "An analysis of adverse events leading to discontinuation, under a heading that describes the analysis" was for discontinuation from treatment or the study and the Division explained that this request was for discontinuation from treatment. Merck agreed to provide the above, for both studies, in their initial submission.

Regarding the minutes (agendas, presentations, and relevant meeting data) from committees overseeing either of the trials, the Division asked the sponsor to ensure that they organize these in a logical manner, group all materials by date, and to include bookmarks. The Division added that if a meeting took place (or was scheduled to take place) and either was cancelled or the minutes were lost to include a place holder in the file noting the situation. All gaps in meeting minutes from any committee should be documented.

7. The Sponsor acknowledges the Agency's request for CRFs and associated documentation. To that end, the Sponsor will provide documents per Table 2 below. Thus, the Sponsor will provide electronic CRFs (eCRFs) and associated queries for subjects who died or discontinued. In addition, the Sponsor will provide the 'adjudication packages' used by the Clinical Endpoints Committee to complete the adjudication eCRFs for these subjects.

With respect to the source documentation used to complete the eCRFs, the Sponsor will not be providing these documents to the Agency as they are part of the subjects' medical charts and are retained at the study sites. Concerning the source documentation used to create Medwatch or CIOMS forms, SAEs were inputted directly by the site into the eCRF and the Academic Research Organization (ARO) safety desks extracted this information from the eCRF and forwarded it to the regional centers which then generated the Medwatch/CIOMS forms. Safety queries generated were submitted by the ARO safety desk or designee and responded to electronically by the study site via the eCRF. Therefore, there is minimal source documentation available beyond the labeled eCRFs. Does the Agency agree with this approach to its request?

#### **FDA Preliminary Response**

No. Please do not limit the submission of CRFs (which includes Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc) to only subjects

that died or discontinued. Please also submit CRFs and queries for all subjects who experienced a SAE. In addition, flag each of discontinuations in a manner that indicates why the subject left the study in the AE and efficacy event tabulations and analysis datasets. Include a field for the date of the patient's last study visit.

Adjudication packages should be submitted for all subjects that had an event adjudicated, not just for "subjects with adjudicated clinical endpoints" (see response #6). Regarding source documents, if these were part of adjudication packages, they should be included in the adjudication package. The adjudication packages we receive as part of the NDA, should be identical to those received by the adjudication committee. Please also provide any adjudication package that was prepared but not sent to the CEC. Within the submission, you should also include the adjudications made by all individual adjudicators, as well as the final adjudication, and information regarding the investigator's assessment of the event.

**Discussion at the Meeting**

Merck asked whether the "CRF-like" documents noted in the parentheses of the above preliminary request was all inclusive list or if these were just examples. Dr. Stockbridge clarified that these were just examples of documents considered "CRFs". He added that some sponsors term CRF as just the page that clinical trial data is collected, but the Agency extends the definition of CRF to documents that capture patient information that is not necessarily directly captured in the clinical database.

Regarding adjudication packages, Dr. Rose emphasized that the packages provided to the FDA should appear exactly as they would have for the adjudication committee. The sponsor acknowledged the Division's comments. Dr. Beasley asked the sponsor whether the individual adjudicators' determinations were available in addition to the final consensus adjudication. The sponsor will confirm that they have each individual's adjudication decision. They agreed to provide the individual results in a dataset, as requested, if available.

The Division asked the sponsor to apply the above request to both TRACER and TRA-2P. The sponsor agreed to provide this in their initial NDA submission.

8. Since both studies were initiated before the effective date of the revised 21 CFR 312.120 (April 28, 2008), the Sponsor is requesting a waiver for 21 CFR 312.120 for the clinical study reports. The table below includes the elements of this waiver for the clinical study reports for both TRA-2°P and TRA\*CER. Does the Agency agree with this waiver?

**FDA Preliminary Response**

Please provide any information you have relevant to the referenced 28 April 2008 guidance.

**Discussion at the Meeting**

The Agency asked for additional time to review this waiver request and that a post-meeting note would be added with the final decision.

**Post-Meeting Note**

The Division confirms that the waivers for #6 and #7 are acceptable. For #9, the Division requests what information the sponsor has on incentives provided to the sites for both TRA\*CER and TRA2°P.

9. Pharmacogenomics

- a. Does the Agency agree with Sponsor's definition of 'poor metabolizers' of clopidogrel responsiveness as alleles including \*2-\*8 (for example, \*2/\*2, \*2/\*3, \*3/\*3, 2/\*4, \*2/\*6, \*2/\*8, \*8/\*8)?

**FDA Preliminary Response**

Yes

**Discussion at the Meeting**

No further discussion.

- b. Does the Agency also agree with Sponsor's definition of 'intermediate metabolizers' as patients with one copy of \*17 or \*1 (for example, \*4/\*17 or \*1/\*5) separate from ultra and extensive metabolizers defined as \*1 and \*17 allele combinations (\*1/\*1, \*17/\*17 or \*1/\*17)?

**FDA Preliminary Response**

Yes, although we prefer that you categorize patients with one poor and one ultrarapid allele (e.g., \*2/\*17) as unknown.

**FDA Additional Comments**

- Please clarify exactly what data will be available (e.g., number of patients with samples available in each arm who received at least one dose and at least seven days).
- Please submit individual genotypes along with linking identifiers to clinical trial datasets as appropriate (or a deidentified efficacy/safety dataset that contains genotypes). Please include consent date and sample collection date and flag if consent was post-randomization. Also, please submit a summary of the genotyping methods and quality control procedures.
- We recommend that you submit data and analyses for all patients who received at least one dose of clopidogrel or vorapaxar rather than seven days as you propose.

**Discussion at the Meeting**

The sponsor asked to provide a written response following the meeting since the appropriate colleague was not in attendance.

**Merck Response to FDA Comments:**

Does FDA want Merck to pull out the unknowns (defined for example as \*2/\*17, \*3/\*17, \*4/\*17, \*6/\*17 or \*8/\*17) as a separate group in the analysis? Please confirm.

Individual data will be provided for patients who met the conditions of (1) being randomized to a study treatment (placebo or vorapaxar), (2) being exposed clopidogrel for at least seven days, and (3) having provided genetic consent. The pharmacogenetic data will include the genetic data connected to treatment and event data for the primary composite endpoint, secondary composite efficacy endpoint, and the GUSTO and TIMI defined safety endpoints in a de-identified manner. The demographic data will also be provided.

In TRA\*CER, there were 9956 patients that met the conditions to be included in the pharmacogenetic analysis. Of those 9956 patients, 5022 were randomized to placebo and

4932 were randomized to the vorapaxar treatment arm. In TRA-2°P, with a total of 4841 patients who met the conditions to be included in the pharmacogenetics analyses, there were 2384 randomized to placebo and 2456 randomized to vorapaxar.

**FDA Post-Meeting Note**

The Division agrees that the unknowns may be analyzed as a separate group as the sponsor proposes.

10. Does the Agency agree that the proposal summarized in the background package will satisfy OSI requirements?

**FDA Preliminary Response**

It is acceptable to omit the financial disclosure information in the summary level dataset, if included in another section of the submission. Please ensure that the financial disclosure information is included in a searchable database.

It is not acceptable to submit only the data related to the location of and contact information for only the sites that are identified for audit by the Office of Scientific Investigations (OSI). Please submit all contact information for all sites in TRACER and TRA-2P. Attached as an appendix to these preliminary responses (Appendix II) is an information request provided by the Office of Scientific Investigations. This document includes data requests that are to be addressed in your initial submission.

**Discussion at the Meeting**

The sponsor explained that they will provide the Agency with contact information for each site, as described in the preliminary comments appendix, but asked whether it was acceptable not to provide sections II and III of the OSI request. The sponsor expressed concern over the amount of time required to prepare these listings due to the number of sites in their Phase 3 trials. The Agency explained that they would have to discuss the request with OSI and provide a post-meeting note with the final decision.

**FDA Post-Meeting Note**

OSI notes that the submission of the 2 datasets requested in Section II and III are not mandatory, however, we encourage the sponsor to submit these data. We are particularly interested in the submission of the dataset described in Section III because this dataset will be used in our pilot "Risk Based Site selection Model." This will enable OSI and the review division to expedite the process of choosing sites for inspection in order that clinical inspections can be conducted in a timely manner for review of your marketing application. This is particularly important for large studies important cardiovascular studies, such as these.

11. Does the Agency concur with Sponsor's plan for submission of the vorapaxar eCTD?

**FDA Preliminary Response**

Yes. When you submit the NDA, please include the following as part of the original submission:

- all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report
- a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived

- the programs that produced all efficacy results and the programs by means of which the derived variables were produced from the raw variables
- a full list of all relevant communications with respect to this development program (IND numbers, serial numbers and submission dates for all protocols, amendments, SAP, meeting minutes)
- minutes of DSMB meetings, if available.

You can check the FDA website to find the information about current document and guidance for study data specifications:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

**Discussion at the Meeting**

No further discussion.

12. If no new vorapaxar safety data are available for submission in a safety update report, does the Agency agree that a SUR will not be required?

**FDA Preliminary Response**

Yes, but please submit a letter to the NDA at the time of the 120-day SUR noting that there is no new data to provide.

**Discussion at the Meeting**

No further discussion.

13. Does the Agency have any comments on the intention of the Sponsor to request a waiver from PREA for the pediatric population at the time of NDA submission, considering the specific adult indication?

**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.

14. Risk Evaluation and Mitigation Strategies

- a. Will the proposed REMS, along with appropriate labeling, satisfy possible Agency's concerns regarding appropriate risk mitigation for vorapaxar's identified risks?

**FDA Preliminary Response**

The REMS you have broadly outlined is in line with the REMS for other cardiovascular products that increase the risk of bleeding. However, the final determination of the adequacy of your proposed REMS is a review question.

**Discussion at the Meeting**

No further discussion.

- b. Does the Agency agree that the content, timing of submission and presentation of the REMS as described in Section 10 will be adequate to allow review of the proposed REMS?

**FDA Preliminary Response**

No. The REMS information you include in Section 8 (not Section 10) states:

“The Sponsor proposes to provide additional supporting materials such as revised and/or additional communication materials that would be aligned to labeling and the methods and measures to be used to assess effectiveness during the review of the application but no later than 90 days prior to the PDUFA date.”

The “additional supporting materials” mentioned above should be included with the original NDA submission

**Discussion at the Meeting**

The sponsor explained that the REMS would be prepared based on final submitted labeling, which is not prepared until close to the time the dossier is submitted. Merck asked whether they could submit the REMS, and the related supporting documents, within 30 days of the initial NDA submission. The Division agreed that this was acceptable.

**2.2. Additional Agency Requests**

1. Tables of components of primary endpoint should include hemorrhagic stroke rate

**Discussion at the Meeting**

The Agency notified the sponsor that this request was applicable to TRACER and TRA-2P. The Division added that any analysis that provided safety related information would be required from both studies. The sponsor agreed to provide these data in the initial NDA submission.

2. Event rates and figures such as the one on p. 17 of your topline results meeting slide set figure should be presented on a per year basis, not a per 3 year basis.

**Discussion at the Meeting**

The Agency notified the sponsor that this request was applicable to TRACER and TRA-2P. Dr. Grant said that although they were requesting the annualized event rate, that sponsors often provide both annualized as well as the event rate for the entire length of the trial.

3. You stratified your randomization and presumably your analyses by PPI use. While that may be a relevant stratification for analyses of bleeding data, you should perform an alternative stratification for analysis of efficacy data – by use of omeprazole or esomeprazole. These two drugs have a significantly greater effect on the metabolism of clopidogrel than other PPIs.

**Discussion at the Meeting**

Merck explained that the randomization was not stratified by PPI, but rather thienopyridine use. The Division acknowledged the sponsor’s clarification, but added that they would still like such an analysis by omeprazole/esomeprazole use. The Division also notified the sponsor that this

request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

4. Provide 30 day post discontinuation rates of key efficacy events and bleeding events (with components of composite endpoints, as in your main tables) in patients who discontinued study drug
  - At any time, i.e., all patients
  - During the treatment period
  - At the scheduled end of the study

If there is a signal of increased event rates with vorapaxar in any analysis, also provide information on event rates during segments of the 30 day period, such as days 1-7, 8-14, and 15-30.

**Discussion at the Meeting**

The Division clarified that all three bullets above were different and that the first bullet was actually a combination of two and three. The sponsor acknowledged the Divisions comments and agreed to provide the analyses. The Division also notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

5. Analyses of time to event (for any event or composite) should censor patients no later than the date of last contact when information was provided with respect to any endpoint included in the analysis. For example, if a patient withdrew consent on date A and there was no later contact with the patient, but the site obtained vital status information only as of date B (which is after date A), analyses involving any endpoint other than death (including composite endpoints that include death along with other endpoints) should be censored no later than date A.

**Discussion at the Meeting**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

6. Patients lost to follow up for any reason during the study (including, e.g., withdrawal of consent or site closure) should be listed in the appropriate early drop category in disposition tables even if the patient is known to be alive at the end of the study.

**Discussion at the Meeting**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

7. Please provide an analysis of the proportion of subjects with complete follow/up. For purposes of this analysis, only subjects who at the conclusion of the trial are known to be dead or for whom all components of the primary endpoint have been ascertained are considered to have complete follow-up. All other subjects should be considered to have incomplete follow-up.

**Discussion at the Meeting**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

8. 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**

Merck explained that the above request would be labor intensive and asked whether this could be provided within the first 30 days of the submission. The Division explained that this was critical data relevant to the primary safety endpoint of the trial and would have to be reviewed quickly upon submission not only for the results but for its level of quality/integrity. The Division did not agree to a late submission of these data.

The Division observed that taking the requisite time to submit a well organized complete NDA is likely to result in a shorter review period. A poorly organized incomplete submission may result in a refusal to file or a complete response.

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

9. 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**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

10. 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**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

11. Please submit MedDRA coding dictionaries for bleeding related AEs, hepatic related AEs, and any other significant AEs for vorapaxar as SAS transport files.

**Discussion at the Meeting**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

12. Please submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the NDA. This table can be placed in the Statistical Review Aid. 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 (and any macros) used to create the table or figure

**Discussion at the Meeting**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

13. Please provide sample clinical trial kits, identical to those used during TRACER and TRA-2P. One kit from each arm should be provided to Ms. Blaus' desk address.

**Discussion at the Meeting**

The sponsor agreed to provide clinical trial kits from each arm of both trials. It was requested that the sponsor provide these to the Division as soon as possible.

14. A description of the responsibilities of each ARO or CRO used in TRACER and TRA-2P.

**Discussion at the Meeting**

The Division notified the sponsor that this request was applicable to TRACER and TRA-2P. The sponsor agreed to provide these data in the initial NDA submission.

15. Please provide the FINAL version of your detailed data management plan, including both manual and programmatic data checks used throughout the study, for both TRACER and TRA-2P. If changes were made during the trial, explain how, when, and the reason the change was instituted. Provide an example of one of your programmatic reports.

**Discussion at the Meeting**

The Division revised the above statement to request ALL versions of the data management plan that were used during the trials. The sponsor agreed to provide these plans in the initial NDA submission.

16. Please provide an encrypted (e.g., with WinZip) copy of the randomization list from TRA-2P. This should be submitted to the IND as soon as possible. Include an unencrypted DEFINE.PDF file describing the variables in the randomization list. Submit the encryption key with the NDA submission.

**Discussion at the Meeting**

The Division requested that the sponsor submit the randomization list as soon as possible to the IND. It was reiterated that the encryption key should still come with the initial NDA submission. The sponsor agreed to comply.

**3.0 OTHER IMPORTANT INFORMATION**

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. Please see Section 2 for that discussion. A list of those items that were agreed to come within 30 days of the original submission are outlined below.

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 a draft REMS (with supporting documents) would be submitted to the NDA and would be in line with the REMS for other cardiovascular products that increase the risk of bleeding. The REMS is expected within 30 days of the initial NDA submission.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application
  - REMS and supporting documents

**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.

**DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

**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 ISSUES REQUIRING FURTHER DISCUSSION

There were a few action items from this preNDA meeting, but all were resolved and noted in the minutes prior to finalizing. Please find their resolution under the Discussion Sections (Section 2).

#### 5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Division agreed to reconsider the sponsor's proposed waivers noted under Question 8	FDA	FDA's response to be included in the final meeting minutes under Question 8
The sponsor stated that they will provide a written response to Question 9 via email, following the meeting	Sponsor	20 June 2012
The Division agreed to follow-up with OSI regarding the sponsor's alternative proposal under Question 10.	FDA	Response from OSI to be included in the final meeting minutes under Question 10

#### 6.0 ATTACHMENTS AND HANDOUTS

There were no handouts or slides provided by the sponsor for this meeting.

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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.**

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/s/

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NORMAN L STOCKBRIDGE  
07/02/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 71384

**MEETING MINUTES**

Merck Sharp & Dohme Corp.  
Attention: Jeffrey Tucker, M.D.  
Senior Director-Worldwide Regulatory Affairs  
P.O. Box 1000, UGC-50  
North Wales, PA 19454

Dear Dr. Tucker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for vorapaxar (SCH 530348).

We also refer to the meeting between representatives of your firm and the FDA on April 25, 2012. The purpose of the meeting was to discuss the results of your two Phase 3 trials, TRACER and TRA-2P.

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, Regulatory Project Manager at (301) 796-1138.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURES:

Meeting Minutes  
Sponsor's Slides

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** C  
**Meeting Category:** Phase 3 Top-Line Meeting  
**Meeting Date and Time:** 25 April 2012; 11am - 12:30pm EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1309  
Silver Spring, Maryland 20903  
**Application Number:** 71384  
**Product Name:** vorapaxar (SCH 530348)  
**Proposed Indication:** reduction of atherothrombotic events in patients with a history of myocardial infarction or peripheral arterial disease  
**Sponsor Name:** Merck Sharp & Dohme Corp.  
**Meeting Chair:** Ellis F. Unger, M.D.  
**Meeting Recorder:** Alison Blas

### FDA ATTENDEES

*\* Office of the Commissioner, Office of International Programs*  
Heidi Janssen European Medicines Agency Fellow  
*\* Office of New Drugs*  
John Jenkins, M.D. Director  
*\* Office of New Drugs, Office of Drug Evaluation I*  
Ellis F. Unger, M.D. Director (acting)  
*\* Office of Drug Evaluation 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  
Martin Rose, M.D. Clinical Reviewer  
Kathie Lillie, M.D. Clinical Reviewer  
Patricia Harlow, Ph.D. Pharmacology/Toxicology  
Edward Fromm, R.Ph., RAC Chief, Regulatory Health Project Manager  
Alison Blas Regulatory Health Project Manager  
*\* Office of Clinical Pharmacology*  
DivyaMenon-Andersen, Ph.D. Reviewer  
Hobart Rodgers, Ph.D. Pharmacogenomics  
*\* Office of Biostatistics*  
Yeh-Fong Chen, Ph.D. Statistician

### SPONSOR ATTENDEES

Barry Gertz, M.D. Global Clinical Development & Regulatory Affairs  
Michael E. Mendelsohn, M.D. Atherosclerosis & CV Research  
Robert J. Meyer, M.D. Global Regulatory Strategy, Policy, & Safety  
John Strony, M.D. Clinical Research  
Francis Platt, M.D. Clinical Research  
Leslie Lipka, Ph.D., M.D. Clinical Research  
Edmond Chen, M.D. Clinical Research  
Bruce Binkowitz, Ph.D. Late Development Statistics

Weili He, Ph.D.	Late Development Statistics
Gail Murphy, M.D.	Project Leader, Cardiovascular
Ekopimo Okon Ibia, M.D., MPH	US Regulatory Policy Lead
Teddy Kosoglou, PharmD	Clinical Pharmacology
Zak Huang, M.D.	Regulatory Affairs
Jeffrey Tucker, M.D.	Regulatory Affairs
* <i>Consultant</i>	
Eugene Braunwald, M.D.	Founding Chairman, TIMI Study Group

## 1.0 BACKGROUND

Vorapaxar, or SCH 530348, is an antagonist of the protease-activated receptor-1 (PAR-1) that inhibits thrombin-induced platelet aggregation. At the End of Phase 2 meeting, minutes dated 16Mar07, the sponsor proposed two trials:

- **TRA-CER** - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome. Patients in this trial were either randomized to placebo or 40mg loading dose of vorapaxar followed by a maintenance dose of 2.5mg.
- **TRA 2P/TIMI 50** - a multinational, multicenter, double blind trial to evaluate the efficacy and safety of vorapaxar in addition to standard of care, compared to placebo in addition to standard of care in the secondary prevention of ischemic events in patients with established atherosclerotic disease, as manifested by coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial disease (PAD). The primary endpoint in this trial was the reduction in the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular death, myocardial infarction (MI), stroke and urgent coronary revascularization. Patients in 2P were randomized to receive either 2.5 mg daily of vorapaxar or matching placebo.

TRACER was stopped early for safety and based on its results, changes were made to the patients enrolled in TIMI 50. TIMI 50 continued in patients who had experienced a previous heart attack or had peripheral arterial disease and the patients admitted into the trial with a history of prior stroke were immediately discontinued.

In 2010, the sponsor discovered salt-to-free base conversion of the drug substance in both the 2.5 mg and the 40 mg SCH 530348 bisulfate immediate-release tablets (both administered in TRACER and TIMI 50). The sponsor claimed that the salt partially converts to the free base during manufacturing and also during storage (depending on packaging and storage conditions), but after some manufacturing changes and a bioequivalence (BE) study conducted in 2011, the sponsor claims that this is no longer a concern. The Agency is currently reviewing the BE, but the sponsor has not submitted the manufacturing changes that have been made to limit the conversion.

This meeting was scheduled to discuss the results from both trials, TRACER and TIMI 50. The sponsor would like to gain the Agency's input on the whether they have strong enough data for a NDA to be filed as well as the narratives, CRFs and any additional analyses that would be needed for such a dossier.

## 2. DISCUSSION

## 2.1. Questions for the Agency

1. Does the Agency agree that data from TRA-2°P study provide sufficient evidence to support filing and review for the following indication?

“TRADEMARK (vorapaxar), an antagonist of the protease activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction or peripheral arterial disease”

### FDA Preliminary Response

Based on the information you provide, we believe that it likely that the data from TRA 2°P and TRA•CER could support filing and review of a NDA for some indication. We have no opinion on the outcome of the NDA review.

### Discussion during the Meeting

No further discussion

2. Given the results of TRA-2P, does the Agency have any comments on the proposed labeling text (proposed indication, dosing and administration, and contraindication)?

### FDA Preliminary Response

Until we review the data from your trials, we cannot definitively comment on your proposed labeling text. However, it is unlikely that we would accept an indication “for the reduction of atherothrombotic events.” In general, we believe it better to name the specific events whose risks are reduced.

### Discussion during the Meeting

No further discussion

3. The data from TRA-2P will be the pivotal study for the NDA submission and TRACER will be a supportive study in the application. Since the data from TRA-2P and TRACER show significant heterogeneity, Merck is proposing not to pool the safety data from these two outcome studies, but to describe the two studies separately in the NDA. Does the Agency agree with this approach?

### FDA Preliminary Response

That proposal appears reasonable.

### Discussion during the Meeting

With the presentation of slides 7 through 16, the sponsor also provided some clarification that was not presented on the slides. It was noted that if a patient had both a stroke and a MI prior to randomization, the patient was qualified on the basis of the MI and not the stroke. Upon presentation of slide 18, the sponsor clarified that although the PAD and CAD arms were discontinued from TRA-2P for safety reasons based on the outcome of TRACER, they were still included in the overall ITT analysis.

In slide 20, Merck explained that the bleeding data from TRA-2P and TRACER will be pooled, but Dr. Rose added that he would also like to see the bleeding data presented in both pooled and separate landmark analyses: time-to-event for bleeding from 2 weeks post-randomization and beyond, and from 30 days post-randomization and beyond. The Division also requested that the bleeding data from the two studies be presented side-by-side.

After presentation of the data captured on the “Efficacy by Time from Qualifying MI” slide, Dr. Grant asked the sponsor to include in the NDA the event rates from the time of randomization through 3 months from the qualifying MI.

The sponsor was then asked when they believed that the indication of “secondary prevention” started. Dr. Braunwald replied that he believed that it started two weeks to a month after the event.

The Division asked the sponsor why there was such an effect on MI in TRA-2P with virtually no effect on mortality. Dr. Braunwald suggested these were analyses by “Total MI” instead of fatal and non-fatal MI. The sponsor said that they will include separate analyses of fatal and non-fatal MI in the NDA. The Division closed the discussion on this slide to state that the results of this trial suggest that the effect of the drug is to prevent MIs at the cost of bleeding, and that sensitivity analyses would be helpful.

4. We propose to prepare narratives on the following patient categories:

- All patients that died
- All patients with an intracranial hemorrhage (ICH)
- All patients with any event of serious bleeding other than ICH (i.e. bleeding meeting GUSTO severe or TIMI major bleeding criteria)
- All patients who discontinued treatment due to a serious adverse event or any bleeding event
- All patients with adverse events of special interest (e.g. thrombocytopenia as defined in the protocols) if not captured in the categories above.

We propose not to prepare narratives for patients if they have only experienced a serious adverse event outside of the categories listed above.

Please note "all patients" includes those on placebo as well as those treated with SCH 530348.

Listings of all serious adverse events will be provided in the report.

Additional narratives will be written should any safety concerns be identified.

Does the Division concur with the following proposal for patient narratives to be provided in the NDA submission?

**FDA Preliminary Response**

We concur.

**Discussion during the Meeting**

No further discussion

5. Per 21CFR 314.50(f) (2) an application is required to contain a copy of the case report form (CRF) of every patient who died or discontinued the study due to an adverse event whether related to treatment or not.

In alignment with the proposal for patient narratives, for the Phase 3 studies, we propose to include in the submission the CRF of a subject in the following categories:

- Every patient who died
- Every patient who discontinued treatment due to a serious adverse event or bleeding event
- All patients with an intracranial hemorrhage (ICH)
- All patients with any event of serious bleeding other than ICH (i.e. bleeding meeting GUSTO severe or TIMI major bleeding criteria)
- All patients with adverse events of special interest (e.g. thrombocytopenia as defined in the protocols) if not captured in the categories above

Additional CRFs would be provided upon Agency request.

Does the Division concur with the following proposal of copies of CRFs to be included in the NDA?

**FDA Preliminary Response**

A major issue in our review of recent outcome trials has been discontinuations attributed to withdrawal of consent. Please describe subject disposition in your presentation.

In your NDA, please plan to include CRFs for all subjects who died or who discontinued for any reason. Please submit CRFs to include all documents containing clinical information collected by the sites or transmitted to you or your agents. CRFs include data queries, adjudication packages, fax coversheets, SAE worksheets, and all other source documents and communications used to complete the labeled CRFs, adjudication packages, and CIOMIS or Medwatch reports.

**Discussion during the Meeting**

No further discussion

**2.2. Additional FDA Requests and Discussion Points**

- If you plan to make a presentation of the results of your trials during our meeting with us, please include the following:
  - In the subgroup of subjects who qualified for enrollment because of a recent MI, Kaplan-Meier estimates of time to the first occurrence of MACE as a function of time between index MI and enrollment. For example, you might dichotomize subjects into those whose index MI occurred more than and less than 3 months prior to enrollment.
  - Discussion of whether the CRFs captured use of clopidogrel at each visit.
  - Discussion of whether the CRFs captured use of omeprazole/esomeprazole or other PPI at each visit
  - The rationale for dose tested.

**Discussion during the Meeting**

Merck presented the slide, “Efficacy (key secondary) and GUSTO Mod/Sev bleeding on baseline PPI use with baseline Thienopyridine use,” to answer some of the Agency’s comments, above. Upon review of the data in the slide, the Agency asked the sponsor to define in the CSR how long a patient would have to be administered a PPI to be categorized as a “PPI user,” and to also detail which PPI each patient used. The sponsor explained that they could detail “PPI use” but the specific PPI used was only captured at baseline in TRA-2P and thus any changes after baseline would not be known.

- PK data

The sponsor confirmed that there were no PK data from TRA-2P and only limited from TRACER. At the end of the study, the sponsor only had samples from approximately 250 patients, with only approximately 40-60 patients with all of the planned time points and on vorapaxar.

- Dosing  
The sponsor based their Phase 3 dosing decision on the Phase 1 and 2 data which suggested that the 1.0 mg and 2.5 mg doses studied in those Phases would get the patient to 80-90% inhibition; the time that the lower dose took was just longer. Dr. Grant asked Merck why they targeted 80-90% inhibition. The sponsor explained that they chose that level primarily based on the data from the IIb/IIIa inhibitors.
- Vital Status  
The investigators in TRA-2P tried to obtain vital status via phone, but the sponsor censored the efficacy analysis at the time of the last office visit. Dr. Marciniak added that the ITT analysis in the dossier should include all data to a common study end date.

### 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 ATTACHMENTS AND HANDOUTS**

Please find attached the slides that were presented at the meeting by the sponsor.

27 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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ELLIS F UNGER  
05/21/2012

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX  
10903 NEW HAMPSHIRE AVE  
BLDG. 22  
SILVER SPRING, MD 20993



**US Mail address:**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266**

**Transmitted via e-mail to:** Deborah Urquhart, Ph.D.

**Company Name:** Schering Corporation

**Phone:** (908) 740-2451

**Subject:** **Minutes of a Meeting w/FDA on  
February 27, 2007  
IND 71,384**

**Date:** March 16, 2007

**Pages including this sheet:** 12

**From:** **Meg Pease-Fye, M.S.**  
**Phone:** **301-796-1130**  
**Fax:** **301-796-9838**  
**E-mail:** **meg.peasefye@fda.hhs.gov**

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

**End of Phase 2 Meeting with Schering Pharmaceuticals**

**Application Number:** IND 71,384  
**Sponsor:** Schering Corporation  
**Drug:** SCH 530348

**Type of Meeting:** End of Phase 2  
**Classification:** Type B

**Teleconference Date:** February 27, 2007  
**Preliminary Responses Sent:** February 23, 2007  
**Confirmation Date:** November 15, 2006  
**Meeting Request Date:** November 8, 2006

**Teleconference Chair:** Robert Temple, M.D.  
**Recorder:** Meg Pease-Fye, M.S.

**List of Attendees:**

Division of Cardiovascular and Renal Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Katharine Lillie, M.D.	Medical Officer
Mehul Mehta, Ph.D.	Director, Division of Clinical Pharmacology I
Peter Hinderling, M.D.	Clinical Pharmacology
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Patricia Harlow, Ph.D.	Pharmacology
James Hung, Ph.D.	Director, Division of Biometrics I
Jialu Zhang, Ph.D.	Statistics
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Division of Anti-Infective and Ophthalmology Products

Wiley Chambers, M.D.	Deputy Division Director
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Schering Corporation

John Petrusis, Ph.D.	Toxicology
Richard Morrissey, Ph.D.	Toxicology
Enrico Veltri, M.D.	Clinical
John Strony, M.D.	Clinical
Gail Berman, M.D.	Clinical
Teddy Kosoglou, Pharm.D.	Clinical Pharmacology
Larisa Reyderman, Ph.D.	Pharmacokinetics and Drug Metabolism
Ron White, Ph.D.	Pharmacokinetics and Drug Metabolism
Ronald Garutti, M.D.	Regulatory
Robert Kowalski, Pharm. D.	Regulatory
Deborah Urquhart, Ph.D.	Regulatory
Gretchen Trout	Regulatory
Michael Perelman, M.D.	Project Direction/Regulatory

Consultant

(b) (4)

**BACKGROUND**

Schering submitted an original IND to the Division on December 17, 2004 for SCH 530348, a platelet inhibitor that binds to PAR-1 receptor. The purpose of this meeting is to obtain Agency input on Schering's proposed Phase 3 trials and ophthalmologic evaluation in humans.

An End of Phase 1 meeting was held with the Division on May 13, 2005. SCH 530348 is indicated for the reduction of thrombotic vascular events in at-risk patients identified by:

(b) (4)

Preliminary responses to Schering's questions were sent on February 23, 2007 and are reproduced below in *italics*. Schering opted to change the face-to-face meeting to a teleconference after receipt of the preliminary responses.

**DISCUSSION**

1. The SCH 530348 doses chosen for Phase 3 are 40 mg as the loading dose and 2.5 mg as the maintenance dose and were determined using a clinically based decision that included pharmacodynamics (inhibition of platelet aggregation) and total safety, including TIMI and non-TIMI bleeding, from the Phase 2 trial and data from earlier, Phase 1 studies.

- The acute loading dose of 40 mg for the ACS trial was selected to achieve a maximum (>80%) and consistent inhibition of TRAP-induced platelet inhibition within a short time i.e. 1 – 2 hours.
- The maintenance dose of 2.5 mg for the ACS and secondary prevention trials was selected
  - o in order to maintain a maximum pharmacodynamic effect, and
  - o to achieve that effect within one week (P04737).

**Does FDA agree with the doses chosen for the Phase 3 studies in ACS (P04736) and secondary prevention (P04737)?**

**Preliminary Response**

*Based on the information provided, it is difficult for reviewers to assess whether the proposed regimen with a loading dose of 40 mg and a maintenance dose of 2.5 mg is optimal. It would be helpful if the PK and PD results from the completed Phase 2 study which lasted 59 days (Phase 1 studies lasted 28 days) would be available. Of interest would be the following information:*

- effective  $t_{1/2}$  (respective fractions of the dose in shallow and deep compartment)

- $C_{min}$  and  $C_{max}$  at steady-state (regimens with and without loading dose)
- relationship between concentration-and platelet aggregation inhibition after collapsing the hysteresis

**Schering's Response:**

In the preliminary PK/PD analysis of the Phase 1 data the observed counter-clockwise hysteresis between plasma SCH 530348 concentration and effect (inhibition of platelet aggregation) has been collapsed and modeled using the effect compartment, representing the active drug concentration at the effect site. The time-dependent aspect of equilibrium between the plasma concentration and effect were characterized by the first-order rate constant  $k_{eo}$  linked to the two-compartment model describing pharmacokinetics of SCH 530348 (Figure 1). Similar PK/PD analysis will be conducted once the data from the Phase 2 study become available.

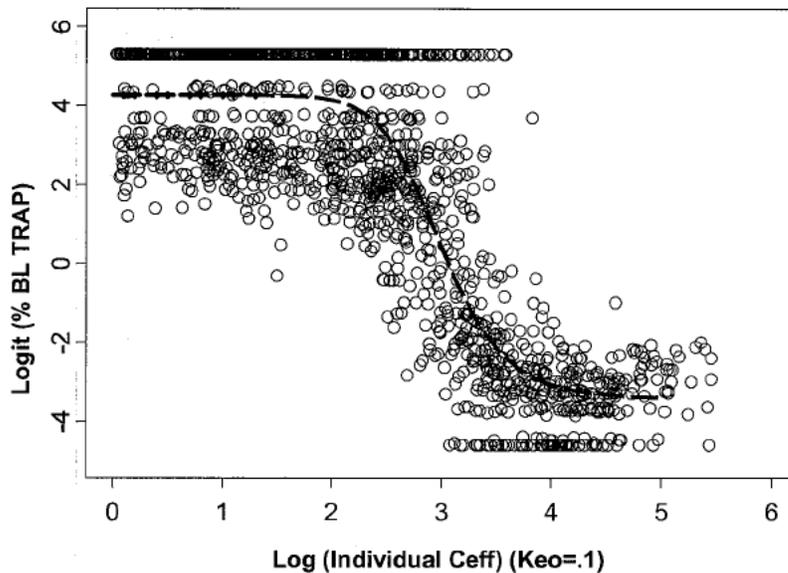


Figure 1. Concentration-effect relationship for SCH 530348 (Data from study P03448)

- mean  $E_{min}$  at steady state (with or without loading dose)
- $E_{rough}$  after loading doses of 10 mg, 20 mg and 40 mg

**Teleconference Discussion:**

PK data from the Phase 2 study are not yet available. Schering anticipates the PK from the Phase 2 study to be comparable to those from Phase 1 studies. PD data was provided in the background package. Schering intends to move the 2.5 mg (maintenance) and 40 mg (loading) doses forward into the Phase 3 trials. The effective half-life of SCH 530348 is pharmacokinetically estimated to be ~100 hours and the platelet inhibition effect time curve indicates that half-life to be ~one week. When Dr. Temple asked if Schering will use a loading dose or a period of daily maintenance to get to effective levels, Schering noted their intention to use a loading dose of SCH 530348 followed by daily maintenance dose in the acute setting, and only daily maintenance dosing in chronic use with no loading dose planned. Since there appears to be no safety signal, Schering believes 2.5 mg can be taken into both their proposed trials. Dr. Stockbridge suggested Schering consider giving a dose that is larger than a single day's dose and use this as a loading dose since the PD data may show the 1 mg to be indistinguishable from the 2.5 mg dose.

Schering responded that a single regimen is easier. They expect to get full pharmacodynamic responses to maximize benefit and get the patients to efficacious levels as soon as possible. Dr. Hinderling argued that a loading dose would provide a fast effect but that a slow association with the target receptor needs to be proportional to the accumulation factor. Schering stated that they were concerned about the possibility of a safety signal. Although the Agency has no major objections to Schering's dosing proposal, Dr. Temple cautioned Schering about the rare event that will not show up until SCH 530348 is administered in a much larger study.

2. **Both P04736 and P04737 are randomized, placebo-controlled trials where SCH 530348 will be administered on top of standard of care. The power of the studies will be based upon the key secondary endpoint of CV death/MI/stroke.**

**Does FDA agree with the endpoints and design of the Phase 3 trials in**

- ACS?
- Secondary Prevention?

**Preliminary Response**

*The Division finds the endpoints and study designs of the Phase 3 ACS and Secondary Prevention trials acceptable.*

**Teleconference Discussion:**

Dr. Stockbridge suggested Schering submit a Special Protocol Assessment when the protocol has been fleshed out for both studies. Schering declined. They intend to begin this study in June and do not wish to spend time on details of protocol negotiations.

3. **For studies P04736 and P04737 the efficacy endpoints and bleeding, as defined below, are the pre-defined events of interest in the protocol and will not be reported by the investigators to the Sponsor as SAEs. They are also expected events in terms of the context of the trial. The DSMB will be responsible for reviewing these events to assure the safety of the patients in the trial. As such, they will not be reported to FDA either as a 15-day alert report or in the annual report.**
  - all-cause death, cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, urgent coronary revascularization occurring  $\geq 30$  days after randomization (P04736 only)
  - moderate and severe bleeding events according to GUSTO criteria
  - TIMI major and minor bleeding, including nonCABG TIMI major and minor bleeding
  - any bleeding that requires rehospitalization or intervention (e.g. transfusion) including intracranial hemorrhage and ischemic stroke with hemorrhagic conversion.

**Does FDA agree with the proposal for not reporting these events as SAEs in Phase 3?**

**Preliminary Response**

*The Division agrees with the proposal for not reporting these events as SAEs in Phase 3 either as a 15-day alert report or in the annual report; however, the Division asks that you submit a detailed description of the DSMB's operating rules.*

**Teleconference Discussion:**

Schering will provide the requested information to the Division.

4. To explore the implication of the rat retinal finding in humans, we are conducting eye exams in the ongoing QTc study and will initiate a specific ocular safety study in healthy subjects. The ocular safety study is expected to run concurrently with Phase 3. In addition, we will conduct appropriate ophthalmologic evaluations in a subset of subjects in the secondary prevention trial.

**Does FDA agree that this approach is appropriate to evaluate the clinical implications of the rat retinal finding?**

**Preliminary Response**

*There is no objection to conducting the proposed ocular safety study in addition to ophthalmic evaluations of a subset of subjects in the secondary prevention trial. It is recommended that for the ocular safety study, the Farnsworth-Munsell (FM) 28, 40 or 100 hue test be used instead of the planned D15 test. There is agreement with the other proposed tests (best corrected distance visual acuity with refraction, slit lamp biomicroscopy, lens photography, dilated fundoscopic examination, fundus photography, Humphrey 30-2 visual field assessment and spectral domain ocular coherence tomography (OCT)).*

*The number of patients being studied in the ocular safety study is small and is not capable of providing a great deal of assurance of ocular safety. The subset of patients from the secondary prevention trial to be studied for ocular safety is recommended to include at least 60 patients who complete treatment and evaluations through at least one year, along with evaluations of the control group. The patients in this subset should have a minimum ophthalmic examination at baseline, month 6 and 12 of best corrected distance visual acuity, FM 28, 40 or 100 hue color vision testing, fundus photography of the central 50 degrees (or 3-7 field 30 degree) and a spectral domain OCT.*

*Please submit the results of the ocular safety study prior to submission of the NDA.*

**Teleconference Discussion:**

Schering has proposed a subset of 1000 patients in their secondary prevention study to receive limited ophthalmic evaluations. Additionally, they proposed a limited eye exam in the secondary prevention study in at least 60 patients and follow them out for one year. Schering asked if the 60 healthy volunteers would replace some portion of the proposed patient subset. Dr. Chambers noted that the Agency would find greater value in having fewer numbers of patients with more exams. Schering should try to rule out a 5% incidence rate, and, as yet, the Agency has no basis to determine what that would be.

Schering asked about an alternative to spectral domain OCT use, since the equipment is not available at all sites. Spectral domain OCT is new technology that has not yet been sufficiently validated with limited availability of machines to do these exams, Schering asked if the Agency would accept OCT without spectral domain. Dr. Chambers agreed.

Dr. Chambers encouraged Schering to make the data from the subset available prior to the submission of the NDA. Schering agreed.

(b) (4)

- *It is critical that you have a clear-cut definition for myocardial infarction (as provided in the Inclusion Criteria for the ACS study)*
- *It may not be necessary to collect all AE data and every concomitant medication in all patients*

(b) (4)

(b) (4)

- *Your statistical plan should be discussed. For you may need to do an Interim Analysis, if probably only for survival. Whether to count every study subject even, if off treatment, should be discussed.*

**Teleconference Discussion:**

A detailed statistical analysis plan should be provided to the Division for review. The trial could conceivably be stopped if the effect on death were negative and positive for the secondary endpoint, or if there were a survival benefit. The study should continue if there were other endpoints, such as silent MIs. Schering asked if patients should continue to be followed even if they are out of the study. The Division stated that yes, they should continue to be followed and be included in the analysis. Schering agreed and will document any events and will follow up with phone calls. Dr. Stockbridge disagreed that telephone follow-up was sufficient since Schering will not meet the criteria for establishing anything other than death. Schering noted they will endeavor to get hospital records. Dr. Temple added that Schering should be aware that if they win on the secondary endpoint and not on the primary endpoints, or if the cardiovascular death, MI and stroke endpoints do not drive the study, then Schering will have a difficult case to make.

(b) (4)

**Additional Preliminary Comments**

- < 2% of radioactivity in the feces is unchanged drug. Since fecal excretion is much larger than renal excretion of radioactivity and there is no evidence of luminal intestinal degradation, SCH 53048 is mainly metabolized (systemically and pre-systemically). You indicate that the main metabolite is an amine which amounts to 18% of the dose? This appears to indicate that there are

a large number of other metabolites that are formed in small quantities? What is the AUC (in mols) of the amine metabolite relative to the parent drug?

- Does the main amine metabolite exhibit pharmacological activity?

**Schering's response:**

SCH 540679 (the amine metabolite of SCH530348) has a PAR-1 Ki of 20 nM in a binding assay using human platelet membranes. In comparison, the PAR-1 Ki for SCH 530348 is 8.5 nM. SCH 540679 transiently inhibited *ex-vivo* platelet aggregation to TRAP in cynomolgus monkeys with maximum inhibition of 55% observed 3 hr post dosing.

SCH 540679 is detected only in trace amounts in plasma following SCH 530348 administration. Thus, it is not considered to be a major human metabolite. Unchanged SCH 530348 is the only major circulating drug-related material in plasma samples collected 2, 6, and 24 hr after dosing.

- What is the metabolic inducer/inhibitor status of SCH 530348?

**Schering's Response:**

The potential for SCH 530348 to inhibit hepatic cytochrome P450 (CYP) isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5 was evaluated using human liver microsomes (pooled from 16 male and female donors) and CYP-specific marker substrates. No metabolism-based inhibition of any of the CYP reactions was observed at SCH 530348 concentrations up to 30  $\mu$ M (14,800 ng/mL). SCH 530348 caused direct inhibition of CYP 2C8 and 2C9 with IC50 values of 1.5  $\mu$ M (739 ng/mL) and 30  $\mu$ M (14,800 ng/mL), respectively. There was also evidence of direct inhibition of 2A6, 2C19, and 2D6; however, the IC50 values were greater than 30  $\mu$ M. Further evaluations of direct inhibition of CYP 2C8 indicated that SCH 530348 is a mixed (competitive-noncompetitive) inhibitor of CYP 2C8 (Ki=0.86  $\mu$ M; 424 ng/mL). Relative to the steady-state C<sub>max</sub> (115 ng/mL) observed following daily 2.5-mg SCH 530348 maintenance dose administration, the I/Ki of 0.27 indicates medium risk potential for CYP 2C8 based drug-drug interaction. Recombinant human CYP 2C8 did not metabolize SCH 530348, suggesting SCH 530348 is not a substrate of this enzyme.

An induction study with human hepatocytes is planned but has not yet initiated; however, no PK or toxicological evidence has thus far emerged from the non-clinical drug safety program to suggest a potential for CYP induction.

- Is SCH 530348 a substrate of MRP2?

**Schering's Response:**

The *in vitro* P-gp substrate/inhibitor studies are underway. A Phase 1 study in healthy volunteers has been conducted to investigate the possibility of drug-drug interaction upon coadministration of SCH 530348 with digoxin, a known P-gp substrate. Coadministration of SCH 530348 with digoxin resulted in a 54% increase in C<sub>max</sub>, but had no effect on AUC(tf) relative to digoxin administration alone. These results indicate that SCH 530348 may be a P-gp inhibitor *in vivo*; however, Schering believes that higher C<sub>max</sub> of digoxin during the distribution phase when administered with versus without concomitant SCH 530348 should have no clinical implication given the equivalent overall exposure to digoxin.

At this time, we have not planned to conduct any studies with MRP2 since SCH 530348 does not fit the expected chemical profile (anionic) for MRP2 substrates. In addition, the carboxylic acid metabolite of

SCH 530348 is not a major human metabolite, and no glucuronide or glutathione metabolites of SCH 530348 have been detected in humans.

- It appears that patients with liver impairment are not excluded from the Phase 3 studies. Please provide rationale.

**Schering's Response:**

SCH 530348 appears to be well-tolerated, and there have been no concerns with hepatic adverse events or LFT abnormalities in healthy volunteers and patients. SCH 530348 is metabolized slowly via CYP3A4 with the resultant metabolite(s) rapidly cleared and eliminated in the feces. Though the relationship between Child Pugh score and CYP 3A4 activity is unclear, we would not expect hepatic impairment to significantly modify TRA exposure more than that observed with ketoconazole; however, given the lack of PK data, we plan to exclude patients with active hepatobiliary disease or ALT and/or AST > 2 X ULN in Phase 3. The liver dysfunction PK study will run in parallel.

- There is no PK program (sparse sampling in a subset of patients) planned for the Phase 3 studies. Please provide rationale.

**Schering's Response:**

No population PK is planned for the Phase 3 study. Schering plans to conduct a population PK analysis based on the sparse data collected in the Phase 2 study.

**CONCLUSION**

- a subset of 1000 patients in their secondary prevention study to receive limited ophthalmic evaluations
- a limited eye exam in the secondary prevention study in at least 60 patients and follow them out for one year
- Schering should try to rule out a 5% incidence rate with the ophthalmic evaluations
- The Agency will accept OCT without spectral domain

**ACTION ITEMS**

- Schering will provide a detailed description of the DSMB's operating rules.
- Schering will provide the Division with a detailed statistical analysis plan for review
- data from the subset of patients receiving ophthalmologic examinations will be available for review prior to the submission of the NDA

Date Minutes Drafted: March 7, 2007  
Date Minutes Finalized: March 16, 2007

Recorder: *{See appended electronic signature page}*  
Meg Pease-Fye, M.S.

Chair Concurrence: *{See appended electronic signature page}*  
Robert Temple, M.D.

Reviewed:

R. Temple	03.15.07
N. Stockbridge	3/13/07
T. Marciniak	3/13/07
K. Lillie	03/13/07
P. Hinderling	03-08-07
A. DeFelice	03-07-07
P. Harlow	03-07-07
J. Hung	3.07.07
J. Zhang	3.07.07

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/s/

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Margaret Pease-Fye  
3/16/2007 03:58:37 PM

Robert Temple  
3/16/2007 05:05:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 71,384

Deborah Urquhart, Ph.D.  
Director, Global Regulatory Affairs  
Schering Corporation  
200 Galloping Hill Road  
Kenilworth, NJ 07033

Dear Dr. Urquhart:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for SCH 530348.

We also refer to your February 27, 2006, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating SCH 530348 as a fast track product (b) (4)

We are granting fast track designation for the following reasons:

1. Cardiovascular disease, as evidenced in patients with acute coronary syndrome or in patients with a history of major cardiovascular deaths, is a serious or life-threatening disease.
2. A drug to reduce cardiovascular morbidity and mortality addresses an unmet medical need.

If you pursue a clinical development program that does not support use of SCH 530348 for reduction of vascular thrombotic events, we will not review the application under the fast track development program.

If you have any questions, please call:

Meg Pease-Fye, M.S.  
Regulatory Health Project Manager  
(301) 796 -1130

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

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

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Norman Stockbridge  
3/17/2006 11:44:35 AM

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 204886

**LATE-CYCLE MEETING MINUTES**

Merck Sharp & Dohme Corp.  
Attention: Chitkala Kalidas, Ph.D.  
Director, Worldwide Regulatory Affairs  
126 E. Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated 10 May 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for vorapaxar sulfate.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on 3 January 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:

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

Sincerely,

*{See appended electronic signature page}*

Thomas Marciniak, M.D.  
Clinical Team Leader  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** 3 January 2014 from 1300 to 1430 EDT  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903  
**Application Number:** NDA 204886  
**Product Name:** vorapaxar sulfate  
**Proposed Indication:** Patients with History of Myocardial Infarction (MI)  
ZONTIVITY (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).  
**Applicant Name:** Merck Sharp & Dohme Corp  
**Meeting Chair:** Thomas Marciniak, M.D.  
**Meeting Recorder:** Alison Blaus, RAC

**FDA ATTENDEES**

**\* Office of Drug Evaluation I**

Ellis Unger, M.D. Director  
Robert Temple, M.D. Deputy Director

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

Norman Stockbridge, M.D., Ph.D. Director  
Mary Ross Southworth, PharmD Safety Deputy Director  
Thomas Marciniak, M.D. Team Leader, Clinical Reviewer  
Martin Rose, M.D., JD Clinical Reviewer  
Jonathan Levine, Ph.D. Clinical Reviewer  
Ed Fromm, RPh, RAC Chief Regulatory Project Manager  
Alison Blaus, RAC Regulatory Health Project Manager

**\* Office of Clinical Pharmacology**

Rajnikanth Madabushi, Ph.D. Team Leader  
Sudharshan Hariharan, Ph.D. Clinical Pharmacology  
Bilal AbuAsal, Ph.D. Clinical Pharmacology  
Fang Li, Ph.D. Pharmacometrics  
Yaning Wang, Ph.D. Team Leader, Pharmacometrics

**\* Office of Biostatistics**

Jim Hung, Ph.D. Director  
Yeh-Fong Chen, Ph.D. Statistician

**\* Office of New Drug Quality Assessment**

Thomas Wong, Ph.D. Reviewer  
Okpo Eradiri, Ph.D. Biopharmaceutics

**\* Office of Surveillance and Epidemiology**

Kimberly Lehrfield, PharmD DRISK Team Leader  
Jamie Wilkins-Parker, PharmD DRISK Reviewer  
Oanh Dang, PharmD Epidemiology

**APPLICANT ATTENDEES**

**\* Merck Sharp & Dohme Corp**

Barry Gertz	Senior Vice President, Clinical Research
Daniel Bloomfield	Vice President, Clinical Research
John Strony	Executive Director, Clinical Research
Gilbert Gleim	Director, Clinical Research
Leslie Lipka	Director, Clinical Research
Christopher Morabito	Associate Director, Clinical Research
Dennis Erb	Senior Vice President, Regulatory Affairs
Scott Korn	Vice President, Regulatory Affairs
Jeff Tucker	Executive Director, Regulatory, Affairs
Chitkala Kalidas	Director, Regulatory Affairs
Lina AlJuburi	Director, Regulatory Policy
Bruce Binkowitz	Executive Director, Biostatistics
Adam Polis, Director	Biostatistics
Weili He, Director	Biostatistics
Yabing Mai	Associate Director, Biostatistics
David Gutstein	Executive Director, Clinical Pharmacology
Matt Anderson	Director, Clinical Pharmacology
Thomas Kerbusch	Executive Director, Pharmacometrics
Ganapathy Mohan	Executive Director, CMC
Jeffrey Ding	Director, CMC
John Petrusis	Director, Toxicology
Dietmar Seiffert	Executive Director, Basic Research/Discovery

**\* TIMI Study Group Participants**

Dr. Eugene Braunwald	Study Chair for TRA 2P study
Dr. David Morrow	Principal Investigator for TRA 2P study

**1.0 BACKGROUND**

NDA 20886 was submitted on 10 May 2013 for ZONTIVITY (vorapaxar sulfate).

Proposed indication: Patients with History of Myocardial Infarction (MI)  
ZONTIVITY (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI).  
ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

PDUFA goal date: 10 May 2014

FDA issued a Background Package in preparation for this meeting on 20 December 2013.

## 2.0 DISCUSSION

### 1. Discussion of Substantive Review Issues

These review issues have both approval and labeling implications so we have expanded upon them below section under 3, Major Labeling Issues.

#### Biostatistics

- During the course of TRA2°P - TIMI 50, there were a number of unplanned interim analyses and some sample size re-estimation that appear to be conducted through the DMC in an unblinded manner. The DMC reviewed not only safety data, but also efficacy, which raises questions about how to interpret the efficacy results.

#### Discussion

The Agency explained that the overall concern was with the number of unplanned interim analyses and their possible impact on the integrity of the trial. Dr. Temple added that we recognized that analyses by a DMC were not uncommon and were generally not a problem as long as there were no protocol changes, but noted it was worthy of discussion at the advisory committee meeting. The applicant explained that these were routine evaluations. Dr. Stockbridge acknowledged the applicant's explanation, but also noted that they overshot the planned number of secondary events substantially. The sponsor responded by explaining that they initially anticipated an 8% aggregated event rate on the primary endpoint and a 4% on the secondary endpoint, but the TIMI group noticed a lower event rate than expected. So in order to maintain their project timelines, the sponsor decided to increase the sample size. Although they anticipated some dropouts, it took longer than expected to get all subjects to complete their last visit, resulting in a much larger number of events than the targeted secondary event number. Dr. Stockbridge concluded this topic by suggesting the applicant present a timeline at the advisory committee meeting with the corresponding analysis results and the decisions made in response to each analysis.

#### Medical

- Vorapaxar, like other antiplatelet and anticoagulant agents, presents a tradeoff between efficacy (reduced atherothrombotic events) and safety (increased bleeding). Traditionally this tradeoff has been evaluated by weighing subjectively separate analyses of safety and efficacy. We believe it would be informative to evaluate vorapaxar benefit/risk by more sophisticated analyses such as net clinical benefit and formal, weighted composite safety and efficacy endpoints.

#### Discussion

No further discussion. The Agency did not request the presentation or discussion of such analyses.

- Your proposal is for approval in a subpopulation of the TRA2P trial, i.e., only in patients with a history of MI excluding patients with a history of stroke or TIA. Accepting subgroup analyses is fraught with dangers of over-interpretation and accepting chance variations as reality. We seek the justification for restricting the indication to this subgroup, particularly considering that there are other post hoc subgroups that have similar benefit/risk profiles. The following should be considered :
  - (a) Eliminating the restriction for ischemic strokes that occurred in some period
  - (b) Eliminating the restriction for TIAs that occurred in some period

- (c) Including PAD patients without a history of MI
- (d) Restricting the indication to patients weighing 60 kg or heavier in addition to or in place of some of the other restrictions
- (e) Including patients with recent ACS (the TRACER population) with the other, justified restrictions for history of stroke, etc.

**Discussion**

The Division asked the applicant why they did not consider adding peripheral artery disease (PAD) to their indication, given that these patients were included in the study and acted much like the coronary artery disease (CAD) patients when patients with prior stroke/TIA were excluded. The Division suggested that patients with PAD should be included in the indicated patient population. The sponsor agreed, but noted that they were less confident with this assessment than CAD/prior history of MI patients, because it was a smaller population. The applicant agreed to revisit the decision and discuss further with the Agency.

Dr. Rose highlighted that when analyzing those patients with a prior history of stroke, there seemed to be a difference in outcome depending upon how far out the patient was from the stroke. That is, a stroke more than 6 months prior to entry did not adversely affect outcome. He acknowledged that there were relatively few such patients. Merck acknowledged this point, but added that they believe a contraindication was appropriate for all patients with a history of stroke, regardless of timing.

The Agency started discussion on the weight restriction topic, noting that the effect of weight < 60 kg on decreasing drug effect seemed substantive, about as great as the effect of prior stroke. These results would seem to need to be discussed in labeling. The applicant asked whether the Agency was trying to demonstrate that low weight and history of stroke were interchangeable in terms of explaining the increased bleeding risk. The Agency explained that they did not think history of stroke and weight were interchangeable, but wanted to highlight the impact when looked at independently. The Agency said that the altered risk/benefit profile in body weight < 60 kg would remain as a topic for the advisory committee and that the Agency would work with the applicant on how to appropriately label the risk.

- There was very little use of the newer approved antiplatelet agents prasugrel and ticagrelor in TRA2P. How this lack of use affects approval and labeling needs to be detailed and justified.

**Discussion**

No further discussion at the late-cycle meeting.

2. Additional Applicant Data

- You are proposing restricting your indication to a subgroup of patients in TRA2P. There are many other subgroups for which vorapaxar safety and/or efficacy vary substantially. For example, subgroup analyses seem to suggest that vorapaxar has little effect or adverse effect on the primary endpoint and the key secondary endpoint in the patients with body weight less than 60 kg, in contrast to the beneficial effect in the patients with body weight 60 kg or above. Your subgroup analyses indicate that GUSTO Severe bleeding rates are higher in the following subgroups than in those not in the named subgroup: weight < 60 kg; weight < study median; women; Asians; and users of clopidogrel at baseline. Our analyses indicate that several of the subgroups listed in the previous sentence are over-represented in the subgroup of persons with body weight < 60 kg, e.g., women and Asians.

To help explain the heterogeneity in labeling, please perform analyses such as multivariate Cox regression analysis, to identify factors that may help to explain the efficacy and safety differences for all relevant subgroups, e.g., qualifying condition, history of stroke, history of TIA, body weight, gender, race, geographic region, and use of medications expected to modify bleeding risk. Explore also elapsed time from the prior stroke as a covariate. Please perform model diagnostics for the models used for such exploratory analyses.

**Discussion**

The requested analysis was provided to the Agency, just prior to the late-cycle meeting. Please see the discussion under the subsection “Discussion of Substantive Review Issues – Medical.”

3. Outstanding Information Requests – 5 minutes (Alison Blaus – RPM)

- 11 December 2013 Information Requests –
  - Survival analysis, based on the investigator determined events, of the primary endpoint, key secondary endpoints, composite of GUSTO Moderate and Severe bleeding. With this analysis, the datasets & SAS code were also requested.
- 13 December 2013 Information Request - samples of the labels, labeling, and packaging (carton-container) for the 5 tablet sample blister pack with the carton and the unit dose blisters with the carton

**Discussion**

The above outstanding information requests were reiterated.

**Post-Meeting Note**

The 11 December 2013 information request has been received, but the 13 December 2013 DMEPA request is still outstanding. DMEPA’s finalized review is awaiting the response of this information request.

4. Discussion of Upcoming Advisory Committee (AC) Meeting – 10 minutes (ALL)

- Discussion of general content of presentations to eliminate potential overlap in Applicant vs. Agency presentations.

**Discussion**

The applicant and the Division committed to providing each other with their advisory committee slides in advance of the AC meeting.

5. Labeling issues – 30 minutes (ALL)

**Discussion**

Please see discussion under section 2.

6. Review Plans – 5 minutes (ALL)

- The review team will briefly discuss those items of the application that are still pending review.

**Discussion**

At the 31 October 2013 Mid-cycle communication meeting, Dr. Marciniak mentioned that he planned to review the neoplasm data in the subsequent months. At the late-cycle meeting, the

applicant asked Dr. Marciniak if he completed his review of neoplasms and whether he had any analyses to share. Dr. Marciniak said that he was not planning on presenting any neoplasm data at the advisory committee, but noted that TRA2P had data much like other trials, but TRACER's data resembled TRITON and that he wanted to review this inconsistency.

7. Wrap-up and Action Items – 5 minutes

**Discussion**

Please see item 4. Both the applicant and the Division committed to providing draft slides in advance of the advisory committee.

**Post-Meeting Note**

Both parties provided final slides in advance of the meeting.

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.

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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.**  
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/s/  
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ALISON L BLAUS  
01/31/2014

THOMAS A MARCINIAK  
01/31/2014



NDA 204886

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Merck Sharp & Dohme Corp.  
Attention: Chitkala Kalidas, Ph.D.  
Director, Worldwide Regulatory Affairs  
126 E. Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for 3 January 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please call:

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

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** 3 January 2014 from 1300 to 1430 EDT  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903  
**Application Number:** NDA 204886  
**Product Name:** vorapaxar sulfate  
**Proposed Indication:** **Patients with History of Myocardial Infarction (MI)**  
ZONTIVITY (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).  
**Applicant Name:** Merck Sharp & Dohme Corp.

### 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

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

##### Biostatistics

- During the course of TRA2°P - TIMI 50, there were a number of unplanned interim analyses and some sample size re-estimation that appear to be conducted through the DMC in an unblinded manner. The DMC reviewed not only safety data, but also efficacy, which raises trial integrity concerns.

### Medical

- Vorapaxar, like other antiplatelet and anticoagulant agents, presents a tradeoff between efficacy (reduced atherothrombotic events) and safety (increased bleeding). Traditionally this tradeoff has been evaluated by weighing subjectively separate analyses of safety and efficacy. We believe it would be informative to evaluate vorapaxar benefit/risk by more sophisticated analyses such as net clinical benefit and formal, weighted composite safety and efficacy endpoints.
- Your proposal is for approval in a subpopulation of the TRA2P trial, i.e., only in patients with a history of MI excluding patients with a history of stroke or TIA. Accepting subgroup analyses is fraught with dangers of over-interpretation and accepting chance variations as reality. We seek the justification for restricting the indication to this subgroup, particularly considering that there are other post hoc subgroups that have similar benefit/risk profiles. The following subgroups need to be evaluated:
  - (a) Your proposed restriction to patients with a history of MI without any history of stroke, TIA, or intracranial hemorrhage
  - (b) Eliminating the restriction for ischemic strokes
  - (c) Eliminating the restriction for TIAs
  - (d) Including PAD patients without a history of MI
  - (e) Restricting to patients weighing 60 kg or heavier in addition to or in place of some of the other restrictions
  - (f) Including patients with recent ACS (the TRACER population) with the other, justified restrictions for history of stroke, etc.
- There was very little use of the newer approved antiplatelet agents prasugrel and ticagrelor in TRA2P. How this lack of use affects approval and labeling needs to be detailed and justified.

These review issues have both approval and labeling implications so we have expanded upon them below section under 3, Major Labeling Issues.

### **3. Major Labeling Issues**

#### Chemistry, Manufacturing, & Controls (CMC)

- As communicated in our 6 December 2013 Advice Letter, your response dated 18 November to our comment on the expression of the strength of the tablet is not acceptable. You should follow the MAPP 5021 and USP <1121> nomenclature for naming the tablet strength. The strength of the tablets should be expressed as our recommendation sent to you in our 4 October advice letter which is:

Trademark (Vorapaxar) Tablets 2.08 mg\*

\*Equivalent to 2.5 mg vorapaxar sulfate

- Due to the conversion of some of the sulfate salt to the free base at the time of manufacture and upon storage, we recommend you to add a statement to the Description (Section 11) of the Package Insert such as "Brand Name tablets are formulated with vorapaxar sulfate, but during manufacture and storage, partial conversion from vorapaxar sulfate to vorapaxar free base may occur".

### Nonclinical

As previously mentioned at the mid-cycle communication meeting, we are recommending that the following items be included in labeling:

- the inclusion of pre/post-natal development results and
- the excretion of vorapaxar into milk

### Clinical Pharmacology

#### 1. *Dosing recommendation for patients*

(b) (4)  
As your proposed label indicated (b) (4), we evaluated the benefit-risk in this subgroup. It can be observed that for the overall population, there is a higher risk for bleeding with vorapaxar compared to control in patients with body weight < 60 kg when compared to patients with body weight ≥ 60 kg [Table 1]. The higher bleeding risk is still evident in the proposed label population. The weight based subgroup analysis showed that the risk for MACE is numerically higher with vorapaxar compared to placebo in patients with body weight < 60 kg for the overall population [Table 2]. Consistent with a higher bleeding risk, the increased risk of MACE in patients with body weight < 60 kg was mainly driven by a higher number of hemorrhagic strokes in the vorapaxar arm compared to placebo. Exclusion of patients with prior history of stroke/TIA within patients post MI mitigated the body weight effect to a certain degree as demonstrated by a lower hazard ratio; however, the point estimate still suggests a numerically increased risk for MACE with vorapaxar compared to placebo [Table 2]. A resampling procedure was performed and the results showed that these findings were highly unlikely due to random chance. We currently envision the following recommendation: Avoid use of vorapaxar in patients with bodyweight < 60 kg.

**Table 1:** Comparison of GUSTO severe or moderate bleeding risk between two body weight subgroups from TRA2°P - TIMI 50

Subgroup	Hazard Ratio [95% CI]	Total sample size
<b>Overall population</b>		
<60 kg	1.87 [1.19-2.94]	1844
≥60 kg	1.48 [1.28-1.73]	24464
<b>Proposed label population</b>		
<60 kg	1.78 [0.85-3.74]	857
≥60 kg	1.46 [1.18-1.80]	15977

**Table 2:** Comparison of primary efficacy endpoint between two body weight subgroups from TRA2°P - TIMI 50

Subgroup	Hazard Ratio [95% CI]	Total sample size
<b>Overall population</b>		
<60 kg	1.28 [0.95-1.73]	1852
≥60 kg	0.86 [0.79-0.93]	24546
<b>Proposed label population</b>		
<60 kg	1.07 [0.69-1.66]	861
≥60 kg	0.80 [0.73-0.89]	16012

2. *Selection of proposed label population*

Prior stroke was considered the most important risk factor for intracranial hemorrhage by the data safety monitoring board and was the first exclusion criterion applied to limit the patient population to achieve a favorable risk/benefit. However, the body weight based subgroup analyses suggested that a similar risk/benefit could be achieved by excluding patients with body weight < 60 kg [Table 3].

**Table 3:** Comparison of efficacy and safety results based on two different subgroups

Endpoint	Subgroup	Hazard Ratio [95% CI]	Total sample size
Efficacy	Post MI and $\geq 60$ kg	0.82 [0.74-0.90]	16836
	Post MI and no prior stroke/TIA	0.82 [0.74-0.90]	16897
GUSTO severe or moderate bleeding	Post MI and $\geq 60$ kg	1.45 [1.18-1.77]	16795
	Post MI and no prior stroke/TIA	1.48 [1.21-1.82]	16856

Further, within the post MI patient population with body weight  $\geq 60$  kg, patients with prior stroke showed numerically better efficacy between vorapaxar and placebo compared to patients without prior stroke/TIA [Table 4]. Despite the small sample size [N=543] in patients with prior stroke, the 95% CI of HR excluded 1, suggesting that vorapaxar showed statistically better efficacy than placebo in this subgroup. The relative risk for GUSTO severe or moderate bleeding events in the prior stroke subgroup is 0.96, indicating that the benefit-risk of vorapaxar in this subgroup is maintained [Table 4].

**Table 4:** The impact of prior stroke, prior TIA on efficacy and safety within patients with post MI and body weight  $\geq 60$  kg

Endpoint	Subgroup	Hazard Ratio [95% CI]	Total sample size
Efficacy	With prior stroke*	0.66 [0.46-0.96]	543
	With prior TIA*	1.56 [0.97-2.5]	357
	Without prior stroke or prior TIA	0.80 [0.73-0.89]	16012
GUSTO severe or moderate bleeding	With prior stroke*	0.96 [0.42-2.17]	540
	With prior TIA*	1.79 [0.66-4.83]	354
	Without prior stroke or prior TIA	1.46 [1.18-1.81]	15977

\*77 patients had both prior stroke and TIA

Based on these analyses, is exclusion of patients with prior stroke in the proposed label population justified?

3. *Use of background antiplatelet agents prior to CABG*

The data you provided in response to our information request about the use/discontinuation of background antiplatelet agents prior to CABG surgery is insufficient. Please provide datasets for patients who underwent CABG surgery in TRACER and TRA2°P - TIMI 50 containing information about (i) vorapaxar use/discontinuation, (ii) background aspirin and/or thienopyridine

use/discontinuation, and (iii) bleeding events. This information will help label the use of vorapaxar prior to CABG.

Medical

1. *Should patients with PAD be included in the indication for vorapaxar?*

TRA 2°P was powered to evaluate the efficacy of vorapaxar for reducing the rate of CV events in the entire study population. It was not powered to evaluate efficacy in the 3 individual atherosclerotic disease-based strata. The PAD stratum made up only 14% of the total patient population, making a statistical significant finding of efficacy in that stratum alone unlikely unless there was a very large beneficial effect.

The benefit of vorapaxar in subjects with PAD is supported by the primary endpoint results in the pooled CAD (prior MI) and PAD strata. In addition, the data suggest a benefit in the PAD stratum alone for the primary efficacy endpoint that is not markedly different in magnitude (in terms of hazard ratio) from the benefit in the CAD stratum (see table below), although the results in the PAD arm alone do not reach statistical significance. Note that the hazard ratio in the in the PAD stratum alone improves when subjects with stroke or TIA are excluded from the analysis, as it does in the CAD stratum.

The data thus suggest that vorapaxar has a beneficial effect on the primary endpoint in patients with PAD. We are curious why you have not included patients with PAD in your proposed indication for vorapaxar. You should be prepared to explain your position at the advisory committee meeting. Please include risk/benefit information in the PAD subgroup that includes information on all-cause mortality, non-fatal stroke and MI, non-fatal GUSTO severe bleeding, ICH not included in previous classifications, and GUSTO moderate bleeding.

**TRA 2°P Primary End Point Results**  
 Events accrued from randomization to last visit

Subgroup (N)*	V vs. P HR (95% CI)	p
All subjects (26,449)	0.88 (0.82 – 0.95)	0.001
No history of stroke (NHS) (20699)	0.86 (0.79 – 0.94)	<0.001
CAD (17779)	0.83 (0.76 - 0.92)	<0.001
CAD, NSH (17191)	0.84 (0.76 – 0.93)	<0.001
CAD, no history of stroke or TIA (NHS/TIA) (16897)	0.82 (0.74 - 0.90)	<0.001
CAD or peripheral arterial disease (PAD) (21566)	0.86 (0.79 - 0.93)	<0.001
CAD or PAD, NHS (20674)	0.86 (0.79 - 0.93)	<0.001
PAD (3787)	0.95 (0.79 - 1.14)	0.567
PAD, NHS (3483)	0.92 (0.76 - 1.12)	0.410
PAD, NHS/TIA (3273)	0.87 (0.71 - 1.06)	0.167

Primary endpoint: Composite of CV death, stroke, MI and urgent coronary revascularization (UCR)

\*CAD and PAD refer to the primary strata based on study-qualifying condition

2. *Does the timing of prior ischemic stroke affect outcomes?*

The Applicant proposes to contraindicate use of vorapaxar in subject with a history of prior stroke (of any kind) or TIA. Subjects with prior intracranial hemorrhage were excluded from TRA 2°P and TRA•CER, as is typical in studies of antiplatelet agents. However, there were many subjects with prior stroke (presumably ischemic) enrolled in TRA 2°P.

Overall, subjects with a prior history of stroke did not have the same observed benefit of vorapaxar as those with no history of stroke:

**TRA 2°P Primary End Point Results in Subjects with and without a Prior Stroke**  
 Events accrued from randomization to last visit

Subgroup (N)	V vs. P HR (95% CI)	p
All subjects (26,449)	0.88 (0.82 – 0.95)	0.001
No history of stroke (20699)	0.86 (0.79 – 0.94)	<0.001
History of stroke* (5646)	0.94 (0.80 - 1.10)	0.465
Prior stroke stratum (4883)	1.02 (0.84 – 1.23)	-
<i>Prior stroke stratum (Key 2° endpoint)</i>	<i>1.03 (0.85 – 1.25)</i>	-

Primary endpoint: Composite of CV death, stroke, MI and UCR

Key Secondary endpoint: Composite of CV death, stroke and MI

\* Regardless of primary stratum

Results for the Key secondary endpoint are shown below for subjects in the prior stroke stratum stratified by time from the most recent stroke to randomization. The data suggest that vorapaxar arm subjects with an ischemic stroke more than 6 months prior to randomization may not have the same risk profile for key secondary endpoint events as those with a stroke closer to randomization.

**TRA 2°P - Effect of Timing of Prior Stroke on Rate of Key Secondary Endpoint <sup>1</sup>**

Subjects in CVD (prior stroke) stratum, stratified by time of most recent stroke to randomization

Time from most recent stroke to randomization (N)	N, KM Rate of Events <sup>1</sup>		V vs. P HR (95% CI)	p
	P	V		
< 3 months (2498)	107, 11.9%	115, 14.4%	1.06 (0.82 – 1.38)	0.66
3 to 6 months (1439)	55, 9.9%	62, 13.8%	1.20 (0.83 – 1.72)	0.33
> 6 months (888)	45, 14.7%	31, 10.1%	0.67 (0.43 – 1.06)	0.09

Key Secondary Endpoint: Composite of CV death, stroke and MI

<sup>1</sup> KM rate is estimate over 1080 days

The HR for the rate of events favors vorapaxar only in subjects with a stroke at least 6 months prior to randomization. However, there are reasons to be skeptical about this finding. First, the >6 month subset is by far the smallest and has the lowest number of events. Also, in that subset, the rate in placebo arm patients is notably higher than in the other two subsets, which is the opposite of what one would expect if the rate of subsequent CV events is reduced over time from a previous stroke. On the other hand, the rate in the > 6 month subset in the vorapaxar arm is lower than the vorapaxar arm rate in the other two subsets.

Finally, the data from the TRITON-TIMI 38 trial of prasugrel vs. clopidogrel in subjects with ACS raise concerns about patients with a stroke more than 1 year before starting treatment with prasugrel. That study showed an increased rate of ischemic stroke and intracranial hemorrhage in subjects in the prasugrel arm compared to control in the subset of subjects with a prior history of stroke. The database included information regarding timing of the prior event with respect to randomization as a binary choice on the CRF: either < 1 year prior or  $\geq$  1 year prior to randomization. The data suggest that the increased risk of stroke with prasugrel vs. control was not lower in those with a prior stroke  $\geq$  1 year before randomization than in those and those with prior stroke < 1 year before randomization, although the absolute rates of stroke in both arms were higher in those with more recent prior stroke and the total number of strokes after randomization in the prior stroke population was small (14, see table below). This relationship may also hold for vorapaxar, even though vorapaxar and prasugrel affect different receptors on platelets and the populations in TRITON and TRA 2°P differed. However, it not clear how many subjects in the TRITON subset with prior stroke < 1 year prior to randomization had a stroke < 6 months prior to randomization, which complicates extrapolation of the TRITON results to the issue of stroke with vorapaxar.

Given the questionable pattern of results in TRA 2°P in the subgroup of subjects with a prior stroke >6 months before randomization and the results of TRITON-TIMI, which suggest a greater risk for prasugrel compared to control regardless of the timing of a prior stroke, it seems prudent to include all patients with a prior history of stroke in whatever contraindication or other limitation of use is included in the labeling of vorapaxar.

Please be prepared to discuss this issue at the Advisory Committee meeting.

**Rates of Ischemic Stroke and Intracranial Hemorrhage during the Study in Subjects in TRITON-TIMI 38 with a Baseline History of Stroke**

<b>Event Type</b>  <b>Period (time from prior stroke to randomization)</b>	<b>Prasugrel</b>  <b>n/N (%)</b>	<b>Clopidogrel</b>  <b>n/N (%)</b>	<b>Incidence Rate Ratio</b>
Ischemic Stroke < 1 year	3/17 (17.6)	1/20 (5.0)	3.5
≥ 1 year	4/164 (2.4)	1/140 (0.7)	3.4
ICH < 1 year	1/17 (5.9)	0/20 (0)	-
≥ 1 year	4/164 (2.4)	0/140 (0)	-
Ischemic Stroke + ICH < 1 year	4/17 (5.9)	1/20 (5.0)	4.7
≥ 1 year	8/164 (2.4)	1/140 (0.7)	6.8

ICH: intracranial hemorrhage

**3. Advisory Committee Meeting**

**Date of AC meeting:** 15 January 2014

**Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management:** 16 December 2013

**Potential questions and discussion topics for AC Meeting are as follows (these are the most recent version):**

1. Vorapaxar, like other antiplatelet and anticoagulant agents, presents a tradeoff between efficacy (reduced atherothrombotic events) and safety (increased bleeding).
  - a) What is the best way to evaluate this tradeoff? Weighing subjectively separate analyses of safety and efficacy? Net clinical benefit analyses? A formal, weighted composite safety and efficacy endpoint?
  - b) Is the benefit/risk evaluation favorable for vorapaxar in TRA2P? (Evaluate subpopulations in response to question 2 next.)
2. The applicant's proposal is for approval in a subpopulation of the TRA2P trial, i.e., only in patients with a history of MI excluding patients with a history of stroke or TIA.

- a) Accepting subgroup analyses is fraught with dangers of over-interpretation and accepting chance variations as reality. What are valid considerations for accepting subgroup results?
- b) The applicant proposes that vorapaxar should not be used by patients with a history of stroke of any kind or TIA.
  - Do you support this general restriction?
  - If use should be avoided in those with a history of ischemic stroke, is the timing of the stroke relevant? If yes, can you state a time relative to the start of treatment before which an ischemic stroke does not rule out use of vorapaxar?
  - Should vorapaxar be used by persons with a history of TIA?
- c) Alternative to applicant's proposal similar benefit-risk can be achieved by restricting the use of vorapaxar in patients with a history of MI weighing 60 kg or heavier (refer Table below).

Endpoint	Subgroup	Hazard Ratio [95% CI]	Total sample size
Efficacy	Post MI and $\geq 60$ kg	0.82 [0.74-0.90]	16836
	Post MI and no prior stroke/TIA	0.82 [0.74-0.90]	16897
GUSTO severe or moderate bleeding	Post MI and $\geq 60$ kg	1.45 [1.18-1.77]	16795
	Post MI and no prior stroke/TIA	1.48 [1.21-1.82]	16856

Do you support this general restriction?

- d) For what subgroups is the benefit/risk evaluation favorable for vorapaxar?
  - Patients with a history of MI without a stroke, TIA, or ICH history as the applicant proposes?
  - Plus patients with PAD without a stroke, TIA, or ICH history?
  - Plus patients with a history of TIA?
  - Plus recent ACS (i.e., the TRACER population) without a stroke, TIA, or ICH history?
  - Patients 60 kg or heavier only?
3. There was very little use of the newer approved antiplatelet agents prasugrel and ticagrelor in TRA2P.
  - a) Does this affect approval?
  - b) If vorapaxar is approved, how should this lack of information be expressed in labeling? As a contraindication? Only in the clinical trials section?
4. Should vorapaxar be approved? For what population?

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>

#### **4. REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## LCM AGENDA

1. Introductory Comments – 5 minutes (Alison Blaus - RPM/ Thomas Marciniak - CDTL)
  - Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 20 minutes (ALL)
  - Each issue will be introduced by the respective FDA reviewer, followed by a discussion.
3. Additional Applicant Data – 10 minutes (ALL)
  - You are proposing restricting your indication to a subgroup of patients in TRA2P. There are many other subgroups for which vorapaxar safety and/or efficacy vary substantially. For example, subgroup analyses seem to suggest that vorapaxar has little effect or adverse effect on the primary endpoint and the key secondary endpoint in the patients with body weight less than 60 kg, in contrast to the beneficial effect in the patients with body weight 60 kg or above. Your subgroup analyses indicate that GUSTO Severe bleeding rates are higher in the following subgroups than in those not in the named subgroup: weight < 60 kg; weight < study median; women; Asians; and users of clopidogrel at baseline. Our analyses indicate that several of the subgroups listed in the previous sentence are over-represented in the subgroup of persons with body weight < 60 kg, e.g., women and Asians.

To help explain the heterogeneity in labeling, please perform analyses such as multivariate Cox regression analysis, to identify factors that may help to explain the efficacy and safety differences for all relevant subgroups, e.g., qualifying condition, history of stroke, history of TIA, body weight, gender, race, geographic region, and use of medications expected to modify bleeding risk. Explore also elapsed time from the prior stroke as a covariate. Please perform model diagnostics for the models used for such exploratory analyses.

4. Outstanding Information Requests – 5 minutes (Alison Blaus – RPM)
  - 11 December 2013 Information Requests –
    - Survival analysis, based on the investigator determined events, of the primary endpoint, key secondary endpoints, composite of GUSTO Moderate and Severe bleeding. With this analysis, the datasets & SAS code were also requested.
  - 13 December 2013 Information Request - samples of the labels, labeling, and packaging (carton-container) for the 5 tablet sample blister pack with the carton and the unit dose blisters with the carton
5. Discussion of Upcoming Advisory Committee Meeting – 10 minutes (ALL)
  - Discussion of general content of presentations to eliminate potential overlap in Applicant vs. Agency presentations.
6. Labeling issues – 30 minutes (ALL)
7. Review Plans – 5 minutes (ALL)
  - The review team will briefly discuss those items of the application that are still pending review.
8. Wrap-up and Action Items – 5 minutes

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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.**  
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/s/  
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ALISON L BLAUS  
12/20/2013

NORMAN L STOCKBRIDGE  
12/20/2013