CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204958Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.5.1 Patent Information

In accordance with 21 CFR 314.53 (c) (1), information about the claimed patent is listed below:

(i) Patent number: 6130208; expiration date: 29 June 2018, and

(ii) Type of patent: active ingredient, composition of matter/Drug and Pharmaceutical composition; methods of use/treatment, and composition of matter/Drug and Pharmaceutical composition; methods of use/treatment

(iii) Name of Patent Owner: Astrazeneca UK Limited; The patent is exclusively licensed by the applicant, The Medicines Company

(iv) AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850

The undersigned declares that Patent No. 6130208 covers the formulation, composition, and/or method of use of (b) (4) (Cangrelor for injection). This product is the subject of this application for which approval is being sought.

THE MEDICINES COMPANY by
Stephen Sherman
Senior Director, Regulatory Affairs

Department of Health and Human Services
Food and Drug Administration

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

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: 204958

NAME OF APPLICANT/NDA HOLDER: The Medicines Company

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)
(b) (4)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Cangrelor	50mg/vial

DOSAGE FORM: Intravenous

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.

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

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6130208	10/10/2000	06/29/2018

d. Name of Patent Owner: Astrazeneca UK Limited

Address *(of Patent Owner)*: 2 Kingdom Street, Paddington
City/State: London, England
ZIP Code: W2 6BD
FAX Number *(if available)*:
Telephone Number: (44) 207604 8000
E-Mail Address *(if available)*:

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)

Astrazeneca Pharmaceuticals LP

Address *(of agent or representative named in 1.e.)*: 1800 Concord Pike
City/State: Wilmington, Delaware
ZIP Code: 19850
FAX Number *(if available)*:
Telephone Number: 302-886-3000
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.**

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?		
8-9		☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

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

Cangrelor for Injection is an intravenous platelet P2Y12 inhibitor for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).

Cangrelor for Injection is indicated to maintain P2Y12 inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery.

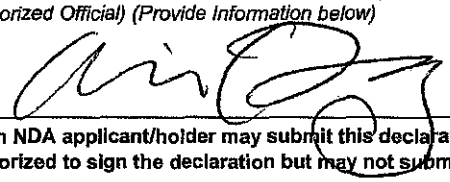
5. No Relevant Patents

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
	2 April 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 Min Ding, Ph.D., Vice President	
Address The Medicines Company 8 Sylvan Way	City/State Parsippany, New Jersey
ZIP Code 07054	Telephone Number (973) 290-6179
FAX Number *(if available)* (973) 207-6179	E-Mail Address *(if available)* min.ding@themedco.com

Department of Health and Human Services
Food and Drug Administration

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

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
204958

NAME OF APPLICANT/NDA HOLDER
The Medicines Company

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)
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ACTIVE INGREDIENT(S)	STRENGTH(S)
Cangrelor	50mg/vial

DOSAGE FORM
Intravenous

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5721219	02/24/1998	02/08/2014

d. Name of Patent Owner
Astrazeneca UK Limited

Address *(of Patent Owner)*
2 Kingdom Street, Paddington

City/State
London, England

ZIP Code
W2 6BD

FAX Number *(if available)*

Telephone Number
(44) 207604 8000

E-Mail Address *(if available)*

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)

Astrazeneca Pharmaceuticals LP

Address *(of agent or representative named in 1.e.)*
1800 Concord Pike

City/State
Wilmington, Delaware

ZIP Code
19850

FAX Number *(if available)*

Telephone Number
302-886-3000

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**.		
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?	
10-12	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

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

Cangrelor for Injection is an intravenous platelet P2Y12 inhibitor for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).

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6. Declaration Certification

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	2 April 2013

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☐ 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 Min Ding, Ph.D., Vice President	
Address The Medicines Company 8 Sylvan Way	City/State Parsippany, New Jersey
ZIP Code 07054	Telephone Number (973) 290-6179
FAX Number *(if available)* (973) 207-6179	E-Mail Address *(if available)* min.ding@themedco.com

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

NDA NUMBER: 204958

NAME OF APPLICANT/NDA HOLDER: The Medicines Company

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TRADE NAME (OR PROPOSED TRADE NAME)
(b) (4)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Cangrelor	50mg/vial

DOSAGE FORM: Intravenous

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6114313	09/05/2000	12/11/2017

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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

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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)* 12	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

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

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	2 April 2013

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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 Min Ding, Ph.D., Vice President	
Address The Medicines Company 8 Sylvan Way	City/State Parsippany, New Jersey
ZIP Code 07054	Telephone Number (973) 290-6179
FAX Number *(if available)* (973) 207-6179	E-Mail Address *(if available)* min.ding@themedco.com

Department of Health and Human Services
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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5955447	09/21/1999	02/08/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Astrazeneca UK Limited	2 Kingdom Street, Paddington	
	City/State: London, England	
	ZIP Code: W2 6BD	FAX Number *(if available)*
	Telephone Number: (44) 207604 8000	E-Mail Address *(if available)*

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.)*	
	1800 Concord Pike	
	City/State: Wilmington, Delaware	
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Astrazeneca Pharmaceuticals LP	Telephone Number: 302-886-3000	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

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2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1, 3-5	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*
	Cangrelor for Injection is an intravenous platelet P2Y12 inhibitor for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). Cangrelor for Injection is indicated to maintain P2Y12 inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery.

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
	2 April 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 Min Ding, Ph.D., Vice President	
Address The Medicines Company 8 Sylvan Way	City/State Parsippany, New Jersey
ZIP Code 07054	Telephone Number (973) 290-6179
FAX Number *(if available)* (973) 207-6179	E-Mail Address *(if available)* min.ding@themedco.com

(b) (4) (Cangrefor for Injection)
1.3.5.2.1 Patent Certification

1.3.5.2 PATENT CERTIFICATIONS

1.3.5.2.1 Patent Numbering: 6130208; expiration date: 29 June 2018

The Medicines Company hereby certifies that the provisions of 21 U.S.C 355 (b)(2) or)j)(2)(A) do not apply to this application.

The Medicines Company hereby certifies US Patent No. 6130208 covers composition of matter/drug and pharmaceutical compositions; methods of use/treatment. This product is the subject of this application for which approval is being sought.

Stephen W Sherman

4/10/2013

Stephen Sherman
Senior Director, Regulatory Affairs

Date

EXCLUSIVITY SUMMARY

NDA # 204958 SUPPL # n/a HFD # 110

Trade Name KENGREAL for Injection

Generic Name cangrelor

Applicant Name The Medicines Company

Approval Date, If Known: TBD

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

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

YES ☐ NO ☒

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

n/a

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

n/a

2. Combination product.

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

YES ☐ NO ☒

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

n/a

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

==========

Name of person completing form: Alison Blaus, RAC
Title: Senior Regulatory Project Manager
Date: 9 June 2015

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

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

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

/s/

ALISON L BLAUS
06/09/2015

NORMAN L STOCKBRIDGE
06/09/2015

DEBARMENT CERTIFICATION

The Medicines Company 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.

Loretta M. Itri, M.D.
EVP Health Science & Regulatory Affairs

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204958 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: KENGREAL Established/Proper Name: cangrelor Dosage Form: Injection		Applicant: The Medicines Company Agent for Applicant (if applicable): n/a
RPM: Alison Blaus, RAC		Division: Cardiovascular & Renal Products

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

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

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

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

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

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

❖ Actions	
• Proposed action • User Fee Goal Date is 23 June 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 30Apr14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

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

❖ Application Characteristics [3]	

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

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

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

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

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

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

Comments: Resubmission after CR

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

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Included
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters: 31Jul13 (denied); 8Oct13 (denied); 8Jan14 (denied); 29Mar14 (accepted) Reviews: 31Jul13; 7Oct13; 6Jan14; 25Mar14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 22Jun15 DMEPA: ☐ None 24Feb15 and 20Mar14 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 10Jun15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None

Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	11Jun13 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC: 20 Nov 2013 (minutes dated 2Dec13) If PeRC review not necessary, explain: n/a	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg 5Aug14 (minutes dated 9Sep14)
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg BRIDGE Topline 8Jun12, BRIDGE pre-NDA 26Dec12, BRIDGE Follow-up Topline 12Sep12; PHOENIX Topline 3Apr13
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 4Aug05 (CHAMPION)
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 21Oct13 (dated 13Nov13)
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 29Jan14 (dated 28Feb14)
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	4Mar14 post-AC meeting (dated 14Apr14)

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

❖ Advisory Committee Meetings	☐ No AC meeting
• Dates of Meetings	12Feb14 and 15Apr15
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 30Apr14 and 22Jun15
Division Director Summary Review *(indicate date for each review)*	☐ None 30Apr14 and 19Jun15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 23Mar14; 28Apr14; 23May14; 28May14; 2Jun14
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	27Jun13 (Filing); 10Jan14 (Marciniak); 13Jan14 (Marciniak); 14Jan14 (Primary); 22Apr14 (Primary addendum); 28Apr14 (Primary addendum); 19Mar15 (Resubmission Primary); 18Jun15 (Resubmission addendum)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	22Apr14 (Primary Clinical Review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	n/a n/a ☐ None 21Jan14 (no REMS needed)
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 29Apr14 and 3Mar15
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review

Statistical Review(s) *(indicate date for each review)*	☐ None 11Jun13 (Filing); 13Jan14 (Primary); 23Apr14 (Primary addendum); 11Mar15 (Resubmission Primary); 25Mar15 (Resubmission addendum)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 18Jun13 (Filing); 10Jan14 (Primary); 15Mar15 (Resubmission Primary)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 25Apr14
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2Jul13 and 10Jan14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None 16Apr14
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 31May13 (CMC Filing); 4Jun13 (Micro Filing); 11Jun13 (Biopharm Filing); 12Dec13 (CMC Primary); 6Jan14 (Micro Primary); 28Mar14 (Biopharm Primary); 15Apr14 (CMC Memo); 17Jun15 (CMC Overview)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None 7Nov13 (Methods Validation Review)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12Dec13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable – See 17Jun15 Quality Review Re-evaluation date: 23Jun15 ☐ Withhold recommendation ☐ Not applicable

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

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

/s/

ALISON L BLAUS
06/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Alison Blaus, ODE 1/DCaRP, (301)796-1138

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
27 May15	56812	204958	(PLEASE CHECK OFF BELOW)

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting):
KENGREAL (cangrelor)	Standard Review – Resubmission after CR	NME	**10 June 2015**

NAME OF FIRM:	
Medicines Company	PDUFA Date: 23 June 2015

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:

EDR Location: \\CDSESUB1\EVSPROD\NDA204958\0000

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: n/a

Labeling Meetings: n/a

Wrap-Up Meeting: n/a

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	X eMAIL ☐ HAND

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

/s/

ALISON L BLAUS
05/27/2015

Lyons, Darrell

From: Lyons, Darrell
Sent: Friday, January 30, 2015 10:47 AM
To: 'Andrew Friedman'
Cc: Jenkins, Darrell; Flowers, Louis; Makela, Cristina; Blaus, Alison
Subject: RE: NDA 204958 (cangrelor): REQUEST SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Hi Andrew,

Since you have decided to keep the previously conditionally acceptable name "Kengreal" no further action is needed at this time.

Thanks,
Darrell

Darrell Lyons, BSN, RN
Commander, USPHS
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092
darrell.lyons@fda.hhs.gov

From: Andrew Friedman [mailto:andrew.friedman@THEMEDCO.com]
Sent: Friday, January 30, 2015 8:26 AM
To: Lyons, Darrell
Cc: Jenkins, Darrell; Flowers, Louis; Makela, Cristina; Blaus, Alison
Subject: RE: NDA 204958 (cangrelor): REQUEST SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Dear Darrell,
Thank you for contacting me. Following the resubmission of the cangrelor NDA and in communication with Alison Blaus from the Division, we have decided to keep the previously conditionally acceptable name "Kengreal" instead of changing it to (b) (4) since there was a much higher likelihood of it being accepted again and lower risk to the timelines. Alison advised that if we stayed with the name "Kengreal" then we would not need to submit anything to support that name (except at some point to submit revised labeling with Kengreal instead of (b) (4)

Please let me know if there is any information that you may need. Is there a timeline for when the FDA confirms Kengreal is still acceptable, since if something has changed it would be important for us to know sooner rather than later.

Many thanks in advance for your consideration.
Andrew

Andrew Friedman, PharmD
Vice President, Global Regulatory Affairs

THE MEDICINES COMPANY®
Office: (973)-290-6027
Mobile: (b) (6)

andrew.friedman@themedco.com

From: Lyons, Darrell [mailto:Darrell.Lyons@fda.hhs.gov]
Sent: Friday, January 30, 2015 8:02 AM
To: Andrew Friedman
Cc: Jenkins, Darrell; Flowers, Louis; Makela, Cristina
Subject: NDA 204958 (cangrelor): REQUEST SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Dear Dr. Friedman,

We have been notified by the Division of Cardiovascular and Renal Products in the Office of New Drugs that you resubmitted your new drug application with the new proposed proprietary name (b) (4) for NDA 204958.

Please refer to our March 29, 2014, Proprietary Name Request Conditionally Acceptable Letter for the proposed proprietary name, KENGREAL, for NDA 204958.

For the new proposed proprietary name, (b) (4) please submit a cover letter to include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold, capital letters on the first page of each submission as outlined in the attached Guidance.

Please click on the link below to read the guidance that describes the information that FDA uses to evaluate proposed proprietary names.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf

If you have any questions or comments, please do not hesitate to contact me.

Thank you,

Darrell

Darrell Lyons, BSN, RN
Commander, USPHS
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092
darrell.lyons@fda.hhs.gov

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/s/

DARRELL LYONS
01/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

The Medicines Company
ATTENTION: Andrew Friedman, PharmD
Vice President, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Friedman:

We acknowledge receipt of your 23 December 2014 resubmission to your new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (cangrelor) for injection.

We consider this a complete, class 2 response to our 30 April 2014 action letter. Therefore, the user fee goal date is 23 June 2015.

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief Project Management Staff
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ALISON L BLAUS
01/07/2015

EDWARD J FROMM
01/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

GENERAL ADVICE

The Medicines Company
ATTENTION: Andrew Friedman, PharmD
Vice President, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Friedman:

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

We also refer to our previous communication dated April 11, 2014 containing our TIMI and GUSTO bleeding classifications. In an effort to further align your and the FDA's bleeding classifications and numbers for CHAMPION PHOENIX, we have prepared the below tables that include those classifications for ACUITY and BARC, and non-CABG bleeding. This document explains how the numbers were reached and how we think they should be presented in labeling

Tables 1-5 lists the subjects that appear discrepant between the FDA and The Medicines Company:

Table 1. FDA Discrepant ACUITY Major Subjects

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401002067	not ACUITY major	ACUITY major	Access site hemorrhage. "Requiring radiologic /surgical intervention" checked. ("manual pressure. Fem stop, sand bag.")
401010006	not ACUITY major	ACUITY major	Access site hemorrhage requiring intervention ("hand held pressure.")
401010171	not ACUITY major	ACUITY major	Hematoma (overt). ISS Hg reduction 3.6 g/dL.
401010226	not ACUITY major	ACUITY major	Hematoma (overt). ISS Hg reduction 3.3 g/dL.
401029038	not ACUITY major	ACUITY major	Hematoma (overt). CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.6 g/dL.
401045038	not ACUITY major	ACUITY major	Hematoma and ecchymosis (overt). ISS Hg reduction 3.3 g/dL.
401053021	not ACUITY major	ACUITY major	Hematoma, oozing (overt). ISS Hg reduction 3.8 g/dL.
401073003	not ACUITY major	ACUITY major	Oozing, "clinically overt" (overt). ISS Hg reduction 3.0 g/dL.

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401091002	not ACUITY major	ACUITY major	Oozing, ecchymosis (overt). ISS Hg reduction 3.0 g/dL.
401091428	not ACUITY major	ACUITY major	Hematoma (overt). ISS Hg reduction 3.0 g/dL.
401091767	not ACUITY major	ACUITY major	Hematoma and ecchymosis (overt). CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.3 g/dL.
401092008	not ACUITY major	ACUITY major	Saphenous vein graft perforation required intervention (overt). ISS Hg reduction 3.5 g/dL.
401092029	not ACUITY major	ACUITY major	Ecchymosis, bloody secretions, "clinically overt",decreased mental status, head CT scan. CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.5 g/dL.
407003032	ACUITY major	not ACUITY major	No source identified. Could qualify based on text box, but not ACUITY major based on ISS lab data
449001022	not ACUITY major	ACUITY major	Access site bleeding requiring intervention "local US guided compression and pressure bandage"
455005012	not ACUITY major	ACUITY major	Ecchymosis (overt). ISS Hg reduction 4.1 g/dL.
459003008	ACUITY major	not ACUITY major	Genitourinary, "clinically overt", prompted evaluation. CRF drop in Hg 3 to ≤ 4 g/dL. ISS Hg reduction disagrees, 1.9 g/dL for the time reported on the bleed CRF.
466001021	not ACUITY major	ACUITY major	transfusion

ISS=Integrated Summary of Safety laboratory dataset

Table 2. FDA Discrepant BARC 3c Subject

CSUBJECT	Applicant's Classification	FDA's Classification	Reason for FDA classification
420009640	BARC 1	BARC 3c	Intracranial hemorrhage

Table 3. FDA Discrepant BARC 3b Subjects

CSUBJECT	Applicant's Classification	FDA's Classification	Reason for FDA classification
401009009	BARC2	BARC3b	Bleeding requiring radiologic or surgical intervention
401012091	BARC2	BARC3b	Led to hospitalization, prompted evaluation, gastrointestinal, heme positive stool (overt). CRF drop in Hg TIMI major. ISS Hg reduction agrees with CRF.
401029051	not classified	BARC3b	Identified from SAE report. Subject with cardiac tamponade and subsequent death.
401030062	BARC2	BARC3b	Hematoma (overt), required intervention, led to hospitalization, transfused. CRF drop in Hg TIMI major. ISS Hg reduction agrees, 5.1 g/dL.
401091615	BARC1	BARC3b	Cardiac tamponade

CSUBJECT	Applicant's Classification	FDA's Classification	Reason for FDA classification
407005090	BARC1	BARC3b	Bleeding requiring radiologic or surgical intervention
407005116	BARC1	BARC3b	GI bleed (overt) with Hg drop gt 5 g/dL
407005124	BARC2	BARC3b	Bleeding requiring surgical intervention per text box field
407005126	BARC2	BARC3b	GI bleed (overt) with Hct drop > 15 %, transfusion
407005127	BARC1	BARC3b	Bleeding requiring radiologic or surgical intervention
420009546	BARC2	BARC3b	Bleeding requiring radiologic or surgical intervention
449014045	BARC3a	BARC3b	Mallory-Weiss rupture, hematemesis (overt), led to hospitalization. Transfused (after 48 hours from drug start). CRF last Hg within 48 hours from drug start is 9.2 g/dL, thus the reduction from baseline is 8.4 g/dL. ISS lab Hg reduction 5.4 g/dL. The Hg in the dataset was collected prior to the bleed time.

Table 4. FDA Discrepant BARC 3a Subjects

Obs	USUBJID	Treatment
1	TMC-CAN-10-01-401010-171	1
2	TMC-CAN-10-01-401010-226	1
3	TMC-CAN-10-01-401010-233	1
4	TMC-CAN-10-01-401011-017	1
5	TMC-CAN-10-01-401028-006	1
6	TMC-CAN-10-01-401029-038	1
7	TMC-CAN-10-01-401030-354	1
8	TMC-CAN-10-01-401045-038	1
9	TMC-CAN-10-01-401045-044	1
10	TMC-CAN-10-01-401053-021	0
11	TMC-CAN-10-01-401073-003	1
12	TMC-CAN-10-01-401079-159	1
13	TMC-CAN-10-01-401091-002	1
14	TMC-CAN-10-01-401091-428	1
15	TMC-CAN-10-01-401091-711	1
16	TMC-CAN-10-01-401091-761	0
17	TMC-CAN-10-01-401091-767	0
18	TMC-CAN-10-01-401092-008	0

Obs	USUBJID	Treatment
19	TMC-CAN-10-01-401092-029	0
20	TMC-CAN-10-01-401097-009	1
21	TMC-CAN-10-01-407005-165	1
22	TMC-CAN-10-01-407007-030	0
23	TMC-CAN-10-01-420001-073	1
24	TMC-CAN-10-01-420009-209	1
25	TMC-CAN-10-01-420009-554	1
26	TMC-CAN-10-01-420009-572	1
27	TMC-CAN-10-01-420009-668	1
28	TMC-CAN-10-01-420009-801	1
29	TMC-CAN-10-01-420019-004	1
30	TMC-CAN-10-01-439009-002	1
31	TMC-CAN-10-01-448001-299	1
32	TMC-CAN-10-01-449004-014	1
33	TMC-CAN-10-01-449017-024	1
34	TMC-CAN-10-01-449017-034	0
35	TMC-CAN-10-01-455005-012	1
36	TMC-CAN-10-01-466001-020	1
37	TMC-CAN-10-01-466001-052	1
38	TMC-CAN-10-01-466002-034	1
39	TMC-CAN-10-01-466002-052	1
40	TMC-CAN-10-01-466002-069	0
41	TMC-CAN-10-01-466005-012	0

Table 5. FDA Discrepant BARC2 Subjects

Obs	USUBJID	Treatment
1	TMC-CAN-10-01-401002-058	0
2	TMC-CAN-10-01-401002-064	0
3	TMC-CAN-10-01-401007-020	1
4	TMC-CAN-10-01-401010-005	1
5	TMC-CAN-10-01-401010-006	1

Obs	USUBJID	Treatment
6	TMC-CAN-10-01-401010-007	0
7	TMC-CAN-10-01-401024-070	0
8	TMC-CAN-10-01-401032-002	1
9	TMC-CAN-10-01-401082-021	1
10	TMC-CAN-10-01-407003-027	0
11	TMC-CAN-10-01-407005-131	1
12	TMC-CAN-10-01-420001-049	1
13	TMC-CAN-10-01-443002-525	0
14	TMC-CAN-10-01-459003-008	0

Table 6 shows the revised non-CABG bleeding classifications.

Table 6. Non-CABG bleeding classification risk at 48 hours in CHAMPION PHOENIX (revised October 2014)

	Cangrelor		Clopidogrel		Cangrelor vs. Clopidogrel		Cangrelor vs. Clopidogrel	
	N=5529	(%)	N=5527	(%)	RR	(95% CI)	OR	(95% CI)
Non CABG bleeds	857[†]	(15.5)	601	(10.9)	1.42	(1.29, 1.56)	1.50	(1.34, 1.67)
GUSTO severe or moderate	32	(0.6)	20	(0.4)	1.57	(0.90, 2.74)	1.57	(0.90, 2.75)
GUSTO severe	10	(0.2)	6	(0.1)	1.64	(0.60, 4.52)	1.64	(0.60, 4.53)
GUSTO severe*	9	(0.2)	6	(0.1)	1.50	(0.53, 4.21)	1.50	(0.53, 4.22)
GUSTO moderate	22	(0.4)	14	(0.3)	1.54	(0.79, 3.00)	1.54	(0.79, 3.01)
GUSTO moderate*	22	(0.4)	13	(0.2)	1.69	(0.85, 3.35)	1.69	(0.85, 3.37)
GUSTO mild	825	(14.9)	581	(10.5)	1.41	(1.28, 1.56)	1.49	(1.33, 1.67)
GUSTO mild*	150	(2.7)	88	(1.6)	1.70	(1.31, 2.21)	1.72	(1.32, 2.25)
TIMI Major or Minor	40	(0.7)	14	(0.3)	2.83	(1.54, 5.19)	2.84	(1.55, 5.23)
TIMI Major	10	(0.2)	5	(0.1)	1.99	(0.68, 5.83)	2.00	(0.68, 5.84)
TIMI Major*	5	(0.1)	5	(0.1)	1.00	(0.29, 3.45)	1.00	(0.29, 3.45)
TIMI Minor	30	(0.5)	9	(0.2)	3.29	(1.56, 6.93)	3.31	(1.57, 6.97)
TIMI Minor*	9	(0.2)	3	(0.1)	3.00	(0.81, 11.07)	3.00	(0.81, 11.10)
Acuity Major	244	(4.4)	144	(2.6)	1.67	(1.37, 2.05)	1.71	(1.39, 2.11)
Barc2	109	(2.0)	66	(1.2)	1.64	(1.21, 2.22)	1.65	(1.21, 2.25)
Barc3a	40	(0.7)	12	(0.2)	3.29	(1.73, 6.26)	3.31	(1.73, 6.31)
Barc3b	19	(0.3)	10	(0.2)	1.86	(0.86, 3.99)	1.86	(0.86, 4.00)
Barc3c	3	(0.1)	1	(0.0)	2.98	(0.31, 28.63)	2.98	(0.31, 28.68)
Bad[‡]	61	(1.1)	41	(0.7)	1.46	(0.99, 2.17)	1.47	(0.99, 2.19)

* Applicant's classification and analysis

[†] Reviewer identified an extra bleed (CSUBJECT 401029051) based on SAE report (no BLD CRF page so subject was excluded from Applicant's report). Classified as GUSTO severe, TIMI major and BARC 3b.

[‡] Bad defined as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization

Reviewer's analysis with factors patient status, gender. Reviewer code: bleed\postAC\primary safety ptstatus gender final. Datasets: raw\bld, iss\fda_bld, iss lab.

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 and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
10/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

MEETING MINUTES

The Medicines Company
ATTENTION: Andrew Friedman, PharmD
Vice President, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Friedman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (cangrelor) for injection.

We also refer to the meeting between representatives of your firm and the FDA on 5 August 2014. The purpose of the meeting was to discuss our 30 April 2014 Complete Response (CR) Letter and your resubmission plans aimed to address the letter.

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

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Post-Complete Response Meeting
Meeting Date and Time:	5 August 2014 from 0930 – 1100 EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 204958
Product Name:	(b) (4) (cangrelor) for injection
Proposed Indications:	**PCI** Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) *[see Clinical Studies (14.1)]*. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel *[see Clinical Studies (14.1)]*. **Bridging** Cangrelor for injection is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery *[see Clinical Studies (14.2)]*.
Applicant Name:	The Medicines Company
Meeting Chair:	Ellis Unger, 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
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Alison Blaus, RAC	Regulatory Health Project Manager
Office of Clinical Pharmacology	
Sreedharan Sabarinath, Ph.D.	Reviewer
Office of Biostatistics, Biometrics I	
Jialu Zhang, Ph.D.	Statistician

APPLICANT ATTENDEES

The Medicines Company

Clive Meanwell, M.D., Ph.D.	Executive Chairman/CEO
Sabrina Comic-Savic	Senior Director, GCP Quality Assurance
Jonathan Day, M.D., Ph.D.	Vice President Medical Director, Global Health Science
Andrew Friedman, PharmD	Vice President, Global Regulatory Strategy
Tiepu Liu, M.D., Ph.D.	Biostatistics, Senior Director, Biostatistics
Sid Senroy	Global Head of Quality
Simona Skerjanec, PharmD, MBA	Team Leader, Senior Vice President
Peter Wijngaard, Ph.D.	Senior Vice President, Global Health Science Leader
Meredith Todd	Vice President, Program Management

Consultants

(b) (4)

1.0 BACKGROUND

Cangrelor for injection is a reversible inhibitor of the platelet P2Y12 receptor belonging to a chemical class and having a mechanism of action different from ticagrelor. The Medicines Company developed cangrelor for the indications listed above and submitted a new drug application (NDA 204948) with the clinical trial data (CHAMPION PCI, CHAMPION PLATFORM, CHAMPION PHOENIX, & BRIDGE) to support these indications on 30 April 2013. This PDUFA V application was reviewed under "The Program". Upon review of the clinical data and a related Advisory Committee Meeting on 12 February 2014, a Complete Response (CR) letter was issued on 30 April 2014.

This meeting was scheduled to discuss the applicant's plan to address the CR Letter and to obtain feedback from the Agency on whether their plan constitutes a complete response to the 30 April 2014 letter.

2. DISCUSSION

Pre-Meeting Preamble

We note that you did not specifically ask about what is probably one of the most critical issues: the period during the transition from cangrelor to clopidogrel when antiplatelet activity is well below the desirable level. We would like to also discuss this at the meeting.

Discussion during the Meeting

Dr. Temple started discussion of this topic by stating that clopidogrel takes at least 2 hours to reach therapeutic effect, even if the loading dose is doubled to 600 mg. Therefore subjects in PHOENIX had a period of at least two hours after cessation of cangrelor infusion during which platelets were inadequately inhibited. Dr. Temple suggested that this would mean that administration of cangrelor delays, but does not eliminate, a time period during which clopidogrel is ineffective. The Medicines Company said that they would provide evidence in the resubmission that this later gap is not important to outcomes, i.e., that there was no excess of events at this later time.

The Division added that it would also be helpful to understand why the applicant chose to study only a 2-hour infusion. Glycoprotein IIb/IIIa inhibitors, which are more potent inhibitors of platelet aggregation than cangrelor, are infused for a much longer time. It is not clear why the duration of infusion for cangrelor should be significantly shorter.

2.1. Questions for the Agency

Intra-Procedural Stent Thrombosis (IPST)

1. Does the Agency agree that the Statistical Analysis Plan satisfies the request "for a more detailed and formal analysis reflecting the issues at the Advisory Committee meeting"?

FDA Preliminary Response

The plan you submitted in the briefing package appears to address the salient concerns expressed at the AC meeting about some components of the composite endpoint in PHOENIX. The Advisory Committee, and we, had considerable skepticism about the clinical meaningfulness of IPST and MIs detected solely on the basis of small increases in biomarkers. We believe that a demonstration of a nominally significant ($p < 0.05$) effect on time to the composite of death, IDR, ARC-ST, and "clinically relevant" periprocedural MI (see response to questions # 5 and 6 for thoughts about clinically relevant periprocedural MI) would help establish the usefulness of administering cangrelor during PCI. However, we still have some concern about the discrepancy in site-reported events (death, MIs noted on the checkbox on the MI CRF, unplanned revascularization or stent thrombosis noted on the checkboxes on the revascularization CRF) and adjudicated events (see our response to question # 7 below).

Discussion during the Meeting

Dr. Meanwell expressed surprise at the outcome of the FDA's review, as he had thought, until January of this year that the application was on track to be approved. Dr. Grant believed the negative vote by the Advisory Committee (AC) was an important consideration, as the AC questioned the utility of the product, the meaningfulness of some of the components of the primary endpoint, and other aspects of the development program, and the applicant did not appear to provide the committee with answers that satisfied them.

Dr. Temple stated the Agency agrees with the applicant that PHOENIX was statistically successful on its primary endpoint. He noted that an analysis of PHOENIX that excludes outcome events whose clinical meaningfulness was questioned by the AC and some of the review staff (i.e., IPST and some periprocedural MIs) was significant with a nominal p-value < 0.05, and that a trial with an active control whose outcome is statistically successful at a p-value < 0.05 is generally considered to constitute adequate evidence of efficacy to support approval of an NDA. The Division opined it was probably not useful to continue discussing the clinical meaningfulness of the questioned components of the primary endpoint (or having an AC discuss them again) because the trial appears successful without including them.

2. Can the Agency comment on MDCO's perspective concerning the acceptability of including IPST as a component of the primary endpoint?

FDA Preliminary Response

We do not believe its inclusion is appropriate. You state that "the time of IPST occurrence is when cangrelor is being administered so it is the most direct test of whether stent thrombosis is reduced by cangrelor" (section 2.1.1.1 of briefing document). We have the following comments:

- IPST is an angiographic biomarker and avoidance of it does not meet the usual definition of a clinical benefit; i.e. improvement in how a patient survives, functions, or feels. IPST may result in the need for additional anti-thrombotic therapy or other intervention, but whether that is a credible benefit depends on the avoided treatment.
- Observational studies (e.g. Brenner et al, 2013) suggest an association between IPST and outcomes, but these data do not reveal whether IPST is itself a cause of the outcomes or an identifier of patients at higher risk for worse outcomes. Also, it could be argued that the lack of survival effect from the PHOENIX trial makes it unlikely that prevention of IPST had an important effect on mortality.
- All 89 CEC-identified IPST events are reported as occurring at the conclusion of coronary angiography and before the start of PCI because the instructions for completion of the case report forms required that the time for all IPST events be reported as occurring before stent placement was initiated. Perhaps the discrepancy in the numbers of events identified by the CEC and the sites is due in part to some CEC-identified events actually occurring before stenting and so appropriately not reported by the sites as IPST.

Discussion during the Meeting
See discussion of Question 1.

3. Intraprocedural stent thrombosis (IPST), like Academic Research Consortium stent thrombosis (ARC-ST), is caused by platelet clumping; however, it captures events that occur at an earlier time during PCI when cangrelor is being administered.

   Can the FDA comment on the top-line results for the sensitivity analyses removing IPST and whether or not FDA believes IPST is a clinically meaningful component of the primary endpoint and as such, can be used for regulatory decision making and labeling?

   FDA Preliminary Response
   As indicated, we doubt that IPST can be used for regulatory decision making or labeling. We note, however, that sensitivity analyses with IPST removed as a component of the primary endpoint at the 48-hour time point show effectiveness.

   Discussion during the Meeting
   See discussion of Question 1.

Periprocedural Myocardial Infarction (MI)

4. Does the Agency agree with the Statistical Analysis Plan to satisfy the request "for a more detailed and formal analysis reflecting the issues at the Advisory Committee meeting"? Specifically,

   - The primary sensitivity analysis for periprocedural MI
   - The supportive sensitivity analysis for periprocedural MI
   - Landmark analyses to demonstrate early procedural effect for all endpoints
   - Kaplan-Meier analyses to address maintenance of cangrelor's effect for all endpoints at 30 days

   FDA Preliminary Response
   See our response to your questions # 1 and # 5.

Discussion during the Meeting
See discussion of Question 1.

5. Can the Agency comment on MDCO's perspective concerning the acceptability of including periprocedural MIs identified solely by creatine kinase-myocardial band isoenzyme (CK-MB) increases of ≥3x (upper limit of normal) ULN?

FDA Preliminary Response
The Division has not developed a consistent position on the threshold of increase in biomarkers of myocardial necrosis in the absence of symptoms or ECG changes required to identify a "clinically relevant" periprocedural MI. Clearly, as noted in an expert consensus document from the Society of Cardiovascular Angiography and Interventions (SCAI) (Moussa et al., 2013, JACC, 62:1563-70), "widespread adoption of a MI definition not clearly linked to subsequent adverse events such as mortality or heart failure may have serious consequences for the appropriate assessment of devices and therapies...."

The report of the Universal Definition of Myocardial Infarction acknowledges that there was no solid scientific basis for defining a biomarker threshold for the diagnosis of periprocedural myocardial infarction (Thygesen et al., 2007, Circulation, 116:2634-2653). The SCAI consensus document referenced above states that "compilation of the best medical evidence to date does not support use of the universal definition as the optimal criterion to identify clinically relevant post-PCI MI events. Rather, most contemporary studies support a post-PCI elevation of CK-MB to ≥10xULN as being clinically relevant". The SCAI developed a consensus definition of clinically relevant periprocedural MI (i.e. linked to subsequent adverse events) in patients with pre-procedure normal baseline troponin and without an acute coronary syndrome (i.e. rising biomarkers not suspected). These include the following:

- CKMB ≥ 10x ULN
- CKMB ≥ 5x ULN where pathological Q waves develop in ≥ 2 contiguous leads (or new persistent LBBB). It is recognized that further study is required to validate the threshold of CKMB ≥ 5x ULN in the setting of new Q waves.
- In the absence of CKMB values, a troponin cTn (I or T) ≥ 70xULN would have similar clinical implications based on a conservative estimate of 7:1 troponin/CKMB ratio (Novack et al., 2012, Arch Intern Med, 172:502-508; Lim et al., 2011, JACC, 57:653-661).
- Troponin cTn (I or T) ≥ 35 ULN plus the development of new pathological Q waves in ≥ 2 contiguous leads or new persistent LBBB.

Similar criteria for clinically relevant periprocedural MI were developed for patients with elevated baseline cardiac biomarkers. These criteria were dependent on documenting peak-level and assessment of serial biomarker levels. The CK-MB and troponin elevation requirements for this patient population were the same as for those patients with normal baseline biomarkers.

Hence while it is unclear what level of periprocedural biomarker increase is clinically relevant, using the conservative SCAI criteria is likely to identify MIs that most or all authorities accept as meaningful.

Discussion during the Meeting
See discussion of Question 1.

6. Can the FDA comment on the top-line results for the sensitivity analyses removing periprocedural MIs identified solely by CK-MB increases of ≥3x ULN and confirm any impact on regulatory decision making and labeling?

FDA Preliminary Response

You propose a sensitivity analysis of the composite of Death/MI/IDR/ARC-ST. You identify events as MIs if the CK-MB≥10xULN, symptoms are present, or ECG changes are present. The nature of the symptoms and type of ECG changes required are not clear. Chest pain alone is not specific enough for substantial myonecrosis to be used as a criterion. During the review, the ECG CRFs in many cases specified the ECG to be abnormal but the descriptor "checkbox" often specified "no criteria apply". It was therefore difficult to interpret some ECGs as ischemic events. Based on our response to question # 5, making use of the best scientific evidence available has prompted our attention to focus on two composite endpoints of interest:

- Death/peri-procedural MI (CK-MB≥10xULN)/IDR/ARC-ST
- Death/periprocedural QWMI or new persistent LBBB (CK-MB≥5x ULN)]/IDR/ARC-ST.

Demonstrating that cangrelor is efficacious in reducing the occurrence of these composite endpoints (the first which you specified in section 3.5.1 of the SAP in your briefing document) would help establish the usefulness of administering cangrelor during PCI.

Discussion during the Meeting

See discussion of Question 1.

Site-Reported Events

7. Can the FDA comment on the top-line results for the sensitivity analyses and confirm any impact on regulatory decision making and labeling?

FDA Preliminary Response

If, as you indicate in Table 6 of the background material for this meeting, the odds ratio for the primary endpoint using CEC-events is similar to that from site-reported events, then it is unlikely that the adjudication process biased the results of PHOENIX.

However, we are somewhat perplexed as to why 63% of the adjudicated endpoint data reported in the CSR were not reported by the sites. We believe the process by which events were identified for adjudication may be an important consideration. In particular, we are interested in understanding changes to the CEC-trigger specification program (see our response to question # 8).

Discussion during the Meeting

The Medicines Company stated that the data in Table 7 in the briefing book were incorrect and that they would follow-up with an amended table after the meeting.

Post-Meeting Clarification

Note from sponsor: "I would like to clarify that the data in Table 7 in the briefing book was not incorrect. Specifically, the data presented on IPST is subject to certain assumptions and what was submitted reflects only the most conservative estimate of the site reported IPST event rates. To clarify this further with the Agency, we propose to submit a comprehensive description of the site vs CEC events in our resubmission. As discussed, before we submit the complete response,

discussing these complex issues either via TC or in person would be very beneficial in ensuring there is clarity."

8. MDCO has conducted an analysis of site-reported events and has demonstrated that it is consistent with the overall results and that concordance with CEC-adjudicated is dependent on the endpoint.

   Can FDA comment on how it views the importance of site-reported versus CEC-reported events?

   FDA Preliminary Response
   The independently conducted CEC-query process bypassed the Investigators' clinical judgment resulting in the incorporation of a significant number of endpoints considered non-relevant or non-validated. The concordance of the point-estimates in the OR for site-reported and CEC-adjudicated endpoints implies that bias was not an issue of concern.

   Discussion during the Meeting
   See discussion of Question 7.

9. MDCO has also done an analysis to characterize the periprocedural MI events identified by the CEC, but not by the site, to show that 40% of these events also have evidence of ischemia (i.e., ECG changes or symptoms of ischemia).

   Can FDA clarify their expectations concerning the implications of the omitted events? Can FDA describe what omitted events are of most concern?

   FDA Preliminary Response
   Missing important events raises concerns about general trial conduct. Although global mega-trials inherently have operational challenges, we expect capture of all endpoint events at the site level pursuant to your Monitoring Plan and Clinical Data Management Plan prior to site closeout and database lock.

   The most concerning features of the PHOENIX trial operations are:

   - Not understanding why investigators did not report clinical endpoints and study monitoring did not identify these endpoints, especially periprocedural MIs with ECG changes or with CK-MB $\geq$10xULN. We also wonder if adverse events were missed, thereby jeopardizing assessment of drug safety.
   - The rationale and process for changes to the CEC-based trigger specification program leading to adjudication of events not reported by the Investigators. We question how many changes may have been made and impact of these changes on the adjudication process. We are concerned about potential adjudication bias or retroactive invalidation of antecedent adjudications as a consequence of altering the adjudication trigger specification program based on reviewed results.

   We expect a clear audit trail in order for us to evaluate:

   - the quality of trial conduct in order to better understand why events were not reported and how to recover potentially unreported adverse events
   - what if any alterations were made to the trigger specification program and how it affected the adjudication

Discussion during the Meeting
No further discussion at the meeting.

CHAMPION-PHOENIX Database Unlock

10. Does the plan for providing documentation on how data integrity was maintained satisfy the Agency's request?

FDA Preliminary Response
Yes, the plan for providing documentation on how data integrity was maintained satisfies the Agency's request.

Discussion during the Meeting
No further discussion at the meeting.

11. Does FDA agree on the presentation of information as seen in the table shells?

FDA Preliminary Response
Yes. However, the patient derived type analysis should include a tabular format as outlined in the CR letter. See our response to question # 14.

Discussion during the Meeting
No further discussion at the meeting.

12. Does FDA need any additional information?

FDA Preliminary Response
No.

Discussion during the Meeting
No further discussion at the meeting.

Bioequivalence of Overencapsulated Clopidogrel to Approved Clopidogrel

13. Does FDA agree that the completed dissolution studies in combination with the data from the Astra-Zeneca bioequivalence (BE) study are appropriate for FDA to judge BE of over-encapsulated clopidogrel clinical supplies to the approved clopidogrel product in the United States (U.S.)?

    If not, what additional documentation or studies are needed?

FDA Preliminary Response
Yes, we agree that the completed dissolution studies in combination with the data from the Astra-Zeneca bioequivalence (BE) study are appropriate for FDA to judge BE of over-encapsulated clopidogrel clinical supplies to the approved clopidogrel product in the United States (U.S.) provided that you also submit the formulation of the over-encapsulated clopidogrel used in this BE study.

Discussion during the Meeting
No further discussion at the meeting.

Clinical Presentation Subgroups

14. The "derived-type" clinical presentation reported in MDCO's subgroup plots is more accurate medically as it uses electronic Case Report Form (eCRF) captured data which represents the most complete clinical picture for each patient at the time of database lock.

    Will the information provided allow FDA to determine if MDCO's classification of clinical presentation is accurate?

    FDA Preliminary Response
    We are uncertain how you determined the "derived-type" is more accurate or even the utility of being "more accurate" for regulatory decision and clinical decision making. The investigators' assessment of clinical presentation as entered in the IVRS at the time of randomization is most likely to reflect the information that a practitioner will have at the time he or she is making the decision about whether to administer cangrelor. Further, investigators were unaware of treatment assignment and the outcomes of PHOENIX when entering clinical presentation whereas you make clear that "derived-type" clinical presentation was determined after study unblinding. The CSR description (section 9.7.1.8.1) of the "derived type" methodology, as well as other documents, failed to discuss key features designed to maintain protocol integrity. Specifically:

    - The SAP is silent on the derivation or use of "derived-type" clinical presentation. We believe that the only pertinent discussion in the SAP is in Section 3.8, which references internal inconsistencies which would be remanded to the Data Manager for further evaluation.
    - Your Data Review Plan adequately described data review tasks (section III) but made no mention about re-classifying entry diagnoses.
    - Your Clinical Data Management Plan described data capture and site personnel resolution of queries based on discrepant data (section IV) but did not describe "derived type" methodology.

    Discussion during the Meeting
    The Division stated they still do not understand how "derived patient type" was determined. The Division concluded that they need a better understanding prior to approval because, at a minimum, a description of outcomes by patient presentation would need to be included in labeling.

Adjunctive Use of Cangrelor in Patients with Stable Angina

15. Does FDA have any comments concerning MDCO's perspective that cangrelor use is supported for PCI patients with stable angina?

    (b) (4) Is there any other data MDCO can provide?

    FDA Preliminary Response
    The use of cangrelor at the time of PCI instead of clopidogrel with clopidogrel started only when cangrelor is stopped results in a period of substantially reduced anti-platelet activity from the time cangrelor is discontinued until the time that clopidogrel becomes fully active. We believe it self-evident that avoidance of this period of reduced anti-platelet activity is desirable and can of course be accomplished by administering clopidogrel some hours prior to PCI without need for cangrelor. Patients undergoing PCI for stable symptoms in the absence of ACS can be administered clopidogrel hours before undergoing PCI because there is no urgency to perform the

procedure. We will need additional explanations of why it is reasonable to delay clopidogrel's use once PCI is planned.

Discussion during the Meeting
See discussion of Question 16.

Relevance of PHOENIX Data to Current American Practice

16. Does FDA have any comments concerning MDCO's perspective that data from PHOENIX are relevant to current American practice?

    If not, what are the implications for labeling? Is there any other data MDCO can provide?

FDA Preliminary Response
While there is no regulatory requirement that the active control in a comparative trial designed to show superiority be best therapy available, the comparator should be reasonably effective and used appropriately as labeled. The most obvious rapidly active effective treatment would have been prasugrel, a drug demonstrated in TRITON to be superior to clopidogrel for prevention of early MIs as well as prevention of stent thrombosis, prasugrel was prohibited although it had been approved for marketing in the USA prior to the initiation of PHOENIX. Apart from not allowing prasugrel, however, control treatment was less than optimal in other ways.

- The use of the most potent and rapid acting anti-platelet drugs available, glycoprotein 2b/3a inhibitors (GPIs), was prohibited except as bailout. We believe that these drugs are not uncommonly used in patients undergoing PCI, especially in patients undergoing PCI during STEMI.
- Administration of clopidogrel at least a few hours prior to PCI increases the anti-platelet effect at the time of PCI because generation of the active metabolite of clopidogrel takes some time. A slide describing when patients in practice were administered clopidogrel relative to PCI was presented at a 2007 Executive Committee meeting for CHAMPION-PCI and PLATFORM. It makes clear that the presenters also believed that "adequate" administration required giving clopidogrel hours before PCI.

We are therefore having difficulty identifying a patient group for whom cangrelor is an appropriate therapeutic choice. We particularly question recommending it for patients with stable angina (see our answer to question # 15).

(b) (4) It seems important for you to explain why you believe that your three studies, particularly in light of the differing outcomes of CHAMPION-PCI CHAMPION-PLATFORM, demonstrate that delaying clopidogrel administration after the start of angioplasty is not harmful to patients.

Discussion during the Meeting
The Division believes the most important issue remaining is identification of a population in whom administration of cangrelor is useful. The Division noted most of the subjects in PHOENIX had stable angina, and that pre-treating patients with clopidogrel (or another platelet P2Y12 receptor blocker) prior to PCI might result in better outcomes than administering cangrelor because the period of ineffective platelet inhibition that follows discontinuation of cangrelor would be avoided. The applicant replied that administration of clopidogrel was commonly delayed in patients with stable angina until delineation of coronary anatomy, in part because it decreases the incidence of bleeding during and after PCI. The Division said that the

applicant would need to provide a persuasive rationale with supportive evidence in the resubmission.

Dr. Temple said that the applicant needs to explain why other oral platelet P2Y12 receptor blockers that work more rapidly were not allowed in PHOENIX and why use of glycoprotein IIb/IIIa inhibitors was prohibited in PHOENIX, other than for bailout.

The Division also suggested that the applicant include a more comprehensive rationale for why the first two CHAMPION trials failed and PHOENIX succeeded. The AC members discussed this topic extensively and appeared not to agree with the applicant's explanations.

(b) (4)

Resubmission Requirements, Review, and Timelines

18. Can FDA provide guidance of how the resubmission should be formatted and any additional requirements (i.e., label update) for the resubmission?

FDA Preliminary Response
There are no additional formatting requirements. You should abide by the guidances for industry, "Classifying Resubmissions in Response to Action Letters" and "Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" before resubmission. Please also include all of the required administrative forms with the resubmission (i.e., debarment certification, labeling, etc.).

(b) (4) (b) (4) please include an updated label in the resubmission.

Discussion during the Meeting
No further discussion at the meeting.

19. Can FDA provide insight into the resubmission review process and timelines?

FDA Preliminary Response
Please see those guidances listed in our preliminary response under Question # 18. Upon receipt of the resubmission of your response to our 30 April 2014 Complete Response Letter, the Agency will meet internally within 14 days to determine if your response constitutes a complete response to all critical aspects of the letter. This decision will be communicated to you within that timeframe. If the resubmission is complete, the application will be reviewed within 6 months of

the receipt date of the submission. Please note that it is likely that a second advisory committee (AC) will take place within month 5 of the review cycle.

Discussion during the Meeting
No further discussion at the meeting.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. If there are any changes to your development plans between the 30 April 2014 Complete Response Letter and your re-submission that would cause your application to trigger PREA, your exempt status would change.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were a number of minor items that due to a lack of time were not discussed. The Division agreed to meet with the applicant to discuss these items via informal teleconference with the primary reviewers and Division management.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The applicant noted that there were errors in Table 7 of the briefing book and committed to providing an amended Table after the meeting. The	Applicant	Post Meeting – Completed

applicant provided the response that appears under Question 7.		

6.0 ATTACHMENTS AND HANDOUTS

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

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

/s/

ELLIS F UNGER
09/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

MEETING PRELIMINARY COMMENTS

The Medicines Company
ATTENTION: Andrew Friedman, PharmD
Vice President, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Friedman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (cangrelor) for injection.

We also refer to your 20 June 2014 correspondence, received 20 June 2014, requesting a meeting to discuss discuss our 30 April 2014 Complete Response (CR) Letter and your resubmission plans aimed to address the letter.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to me, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	A
Meeting Category:	Post Complete Response Meeting
Meeting Date and Time:	5 August 2014 from 0930 – 1100 EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 204958
Product Name:	(b) (4) (cangrelor) for injection
Proposed Indications:	**PCI** Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) *[see Clinical Studies (14.1)]*. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel *[see Clinical Studies (14.1)]*. **Bridging** Cangrelor for injection is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery *[see Clinical Studies (14.2)]*.
Applicant Name:	The Medicines Company

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for 5 August 2014 at FDA Headquarters between The Medicines Company and the Division of Cardiovascular & Renal Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-

meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Cangrelor for injection is a reversible inhibitor of the platelet P2Y12 receptor belonging to a chemical class and having a mechanism of action different from ticagrelor. The Medicines Company developed cangrelor for the indications listed above and submitted a new drug application (NDA 204948) with the clinical trial data (CHAMPION PCI, CHAMPION PLATFORM, CHAMPION PHOENIX, & BRIDGE) to support these indications on 30 April 2013. This PDUFA V application was reviewed under "The Program". Upon review of the clinical data and a related Advisory Committee Meeting on 12 February 2014, a Complete Response (CR) letter was issued on 30 April 2014.

This meeting was scheduled to discuss the applicant's plan to address the CR Letter and to obtain feedback from the Agency on whether their plan constitutes a complete response to the 30 April 2014 letter.

2.0 DISCUSSION

We note that you did not specifically ask about what is probably one of the most critical issues: the period during the transition from cangrelor to clopidogrel when antiplatelet activity is well below the desirable level. We would like to also discuss this at the meeting.

2.1. Questions for the Agency

Intra-Procedural Stent Thrombosis (IPST)

1. Does the Agency agree that the Statistical Analysis Plan satisfies the request "for a more detailed and formal analysis reflecting the issues at the Advisory Committee meeting"?

FDA Preliminary Response

The plan you submitted in the briefing package appears to address the salient concerns expressed at the AC meeting about some components of the composite endpoint in PHOENIX. The Advisory Committee, and we, had considerable skepticism about the clinical meaningfulness of IPST and MIs detected solely on the basis of small increases in biomarkers. We believe that a demonstration of a nominally significant ($p < 0.05$) effect on time to the composite of death, IDR, ARC-ST, and "clinically relevant" periprocedural MI (see response to questions # 5 and 6 for thoughts about clinically relevant periprocedural MI) would help establish the usefulness of administering cangrelor during PCI. However, we still have some concern about the discrepancy in site-reported events (death, MIs noted on the checkbox on the MI CRF, unplanned revascularization or stent thrombosis noted on the checkboxes on the revascularization CRF) and adjudicated events (see our response to question # 7 below).

2. Can the Agency comment on MDCO's perspective concerning the acceptability of including IPST as a component of the primary endpoint?

   FDA Preliminary Response
   We do not believe its inclusion is appropriate. You state that "the time of IPST occurrence is when cangrelor is being administered so it is the most direct test of whether stent thrombosis is reduced by cangrelor" (section 2.1.1.1 of briefing document). We have the following comments:

   - IPST is an angiographic biomarker and avoidance of it does not meet the usual definition of a clinical benefit; i.e. improvement in how a patient survives, functions, or feels. IPST may result in the need for additional anti-thrombotic therapy or other intervention, but whether that is a credible benefit depends on the avoided treatment.
   - Observational studies (e.g. Brenner et al, 2013) suggest an association between IPST and outcomes, but these data do not reveal whether IPST is itself a cause of the outcomes or an identifier of patients at higher risk for worse outcomes. Also, it could be argued that the lack of survival effect from the PHOENIX trial makes it unlikely that prevention of IPST had an important effect on mortality.
   - All 89 CEC-identified IPST events are reported as occurring at the conclusion of coronary angiography and before the start of PCI because the instructions for completion of the case report forms required that the time for all IPST events be reported as occurring before stent placement was initiated. Perhaps the discrepancy in the numbers of events identified by the CEC and the sites is due in part to some CEC-identified events actually occurring before stenting and so appropriately not reported by the sites as IPST.

3. Intraprocedural stent thrombosis (IPST), like Academic Research Consortium stent thrombosis (ARC-ST), is caused by platelet clumping; however, it captures events that occur at an earlier time during PCI when cangrelor is being administered.

   Can the FDA comment on the top-line results for the sensitivity analyses removing IPST and whether or not FDA believes IPST is a clinically meaningful component of the primary endpoint and as such, can be used for regulatory decision making and labeling?

   FDA Preliminary Response
   As indicated, we doubt that IPST can be used for regulatory decision making or labeling. We note, however, that sensitivity analyses with IPST removed as a component of the primary endpoint at the 48-hour time point show effectiveness.

Periprocedural Myocardial Infarction (MI)

4. Does the Agency agree with the Statistical Analysis Plan to satisfy the request "for a more detailed and formal analysis reflecting the issues at the Advisory Committee meeting"? Specifically,

   - The primary sensitivity analysis for periprocedural MI
   - The supportive sensitivity analysis for periprocedural MI
   - Landmark analyses to demonstrate early procedural effect for all endpoints
   - Kaplan-Meier analyses to address maintenance of cangrelor's effect for all endpoints at 30 days

FDA Preliminary Response
See our response to your questions # 1 and # 5.

5. Can the Agency comment on MDCO's perspective concerning the acceptability of including periprocedural MIs identified solely by creatine kinase-myocardial band isoenzyme (CK-MB) increases of ≥3x (upper limit of normal) ULN?

FDA Preliminary Response
The Division has not developed a consistent position on the threshold of increase in biomarkers of myocardial necrosis in the absence of symptoms or ECG changes required to identify a "clinically relevant" periprocedural MI. Clearly, as noted in an expert consensus document from the Society of Cardiovascular Angiography and Interventions (SCAI) (Moussa et al., 2013, JACC, 62:1563-70), "widespread adoption of a MI definition not clearly linked to subsequent adverse events such as mortality or heart failure may have serious consequences for the appropriate assessment of devices and therapies...."

The report of the Universal Definition of Myocardial Infarction acknowledges that there was no solid scientific basis for defining a biomarker threshold for the diagnosis of periprocedural myocardial infarction (Thygesen et al., 2007, Circulation, 116:2634-2653). The SCAI consensus document referenced above states that "compilation of the best medical evidence to date does not support use of the universal definition as the optimal criterion to identify clinically relevant post-PCI MI events. Rather, most contemporary studies support a post-PCI elevation of CK-MB to ≥10xULN as being clinically relevant". The SCAI developed a consensus definition of clinically relevant periprocedural MI (i.e. linked to subsequent adverse events) in patients with pre-procedure normal baseline troponin and without an acute coronary syndrome (i.e. rising biomarkers not suspected). These include the following:

- CKMB ≥ 10x ULN
- CKMB ≥ 5x ULN where pathological Q waves develop in ≥ 2 contiguous leads (or new persistent LBBB). It is recognized that further study is required to validate the threshold of CKMB ≥ 5x ULN in the setting of new Q waves.
- In the absence of CKMB values, a troponin cTn (I or T) ≥ 70xULN would have similar clinical implications based on a conservative estimate of 7:1 troponin/CKMB ratio (Novack et al., 2012, Arch Intern Med, 172:502-508; Lim et al., 2011, JACC, 57:653-661).
- Troponin cTn (I or T) ≥ 35 ULN plus the development of new pathological Q waves in ≥ 2 contiguous leads or new persistent LBBB.

Similar criteria for clinically relevant periprocedural MI were developed for patients with elevated baseline cardiac biomarkers. These criteria were dependent on documenting peak-level and assessment of serial biomarker levels. The CK-MB and troponin elevation requirements for this patient population were the same as for those patients with normal baseline biomarkers.

Hence while it is unclear what level of periprocedural biomarker increase is clinically relevant, using the conservative SCAI criteria is likely to identify MIs that most or all authorities accept as meaningful.

6. Can the FDA comment on the top-line results for the sensitivity analyses removing periprocedural MIs identified solely by CK-MB increases of ≥3x ULN and confirm any impact on regulatory decision making and labeling?

FDA Preliminary Response

You propose a sensitivity analysis of the composite of Death/MI/IDR/ARC-ST. You identify events as MIs if the CK-MB≥10xULN, symptoms are present, or ECG changes are present. The nature of the symptoms and type of ECG changes required are not clear. Chest pain alone is not specific enough for substantial myonecrosis to be used as a criterion. During the review, the ECG CRFs in many cases specified the ECG to be abnormal but the descriptor "checkbox" often specified "no criteria apply". It was therefore difficult to interpret some ECGs as ischemic events. Based on our response to question # 5, making use of the best scientific evidence available has prompted our attention to focus on two composite endpoints of interest:

- Death/peri-procedural MI (CK-MB≥10xULN)/IDR/ARC-ST
- Death/periprocedural QWMI or new persistent LBBB (CK-MB≥5x ULN)]/IDR/ARC-ST.

Demonstrating that cangrelor is efficacious in reducing the occurrence of these composite endpoints (the first which you specified in section 3.5.1 of the SAP in your briefing document) would help establish the usefulness of administering cangrelor during PCI.

Site-Reported Events

7. Can the FDA comment on the top-line results for the sensitivity analyses and confirm any impact on regulatory decision making and labeling?

   FDA Preliminary Response

   If, as you indicate in Table 6 of the background material for this meeting, the odds ratio for the primary endpoint using CEC-events is similar to that from site-reported events, then it is unlikely that the adjudication process biased the results of PHOENIX.

   However, we are somewhat perplexed as to why 63% of the adjudicated endpoint data reported in the CSR were not reported by the sites. We believe the process by which events were identified for adjudication may be an important consideration. In particular, we are interested in understanding changes to the CEC-trigger specification program (see our response to question # 8).

8. MDCO has conducted an analysis of site-reported events and has demonstrated that it is consistent with the overall results and that concordance with CEC-adjudicated is dependent on the endpoint.

   Can FDA comment on how it views the importance of site-reported versus CEC-reported events?

   FDA Preliminary Response

   The independently conducted CEC-query process bypassed the Investigators' clinical judgment resulting in the incorporation of a significant number of endpoints considered non-relevant or non-validated. The concordance of the point-estimates in the OR for site-reported and CEC-adjudicated endpoints implies that bias was not an issue of concern.

9. MDCO has also done an analysis to characterize the periprocedural MI events identified by the CEC, but not by the site, to show that 40% of these events also have evidence of ischemia (i.e., ECG changes or symptoms of ischemia).

Can FDA clarify their expectations concerning the implications of the omitted events? Can FDA describe what omitted events are of most concern?

FDA Preliminary Response
Missing important events raises concerns about general trial conduct. Although global mega-trials inherently have operational challenges, we expect capture of all endpoint events at the site level pursuant to your Monitoring Plan and Clinical Data Management Plan prior to site closeout and database lock.

The most concerning features of the PHOENIX trial operations are:

- Not understanding why investigators did not report clinical endpoints and study monitoring did not identify these endpoints, especially periprocedural MIs with ECG changes or with CK-MB $\geq$10xULN. We also wonder if adverse events were missed, thereby jeopardizing assessment of drug safety.
- The rationale and process for changes to the CEC-based trigger specification program leading to adjudication of events not reported by the Investigators. We question how many changes may have been made and impact of these changes on the adjudication process. We are concerned about potential adjudication bias or retroactive invalidation of antecedent adjudications as a consequence of altering the adjudication trigger specification program based on reviewed results.

We expect a clear audit trail in order for us to evaluate:

- the quality of trial conduct in order to better understand why events were not reported and how to recover potentially unreported adverse events
- what if any alterations were made to the trigger specification program and how it affected the adjudication

CHAMPION-PHOENIX Database Unlock

10. Does the plan for providing documentation on how data integrity was maintained satisfy the Agency's request?

    FDA Preliminary Response
    Yes, the plan for providing documentation on how data integrity was maintained satisfies the Agency's request.

11. Does FDA agree on the presentation of information as seen in the table shells?

    FDA Preliminary Response
    Yes. However, the patient derived type analysis should include a tabular format as outlined in the CR letter. See our response to question # 14.

12. Does FDA need any additional information?

    FDA Preliminary Response
    No.

Bioequivalence of Overencapsulated Clopidogrel to Approved Clopidogrel

13. Does FDA agree that the completed dissolution studies in combination with the data from the Astra-Zeneca bioequivalence (BE) study are appropriate for FDA to judge BE of over-encapsulated clopidogrel clinical supplies to the approved clopidogrel product in the United States (U.S.)?

    If not, what additional documentation or studies are needed?

    FDA Preliminary Response
    Yes, we agree that the completed dissolution studies in combination with the data from the Astra-Zeneca bioequivalence (BE) study are appropriate for FDA to judge BE of over-encapsulated clopidogrel clinical supplies to the approved clopidogrel product in the United States (U.S.) provided that you also submit the formulation of the over-encapsulated clopidogrel used in this BE study.

Clinical Presentation Subgroups

14. The "derived-type" clinical presentation reported in MDCO's subgroup plots is more accurate medically as it uses electronic Case Report Form (eCRF) captured data which represents the most complete clinical picture for each patient at the time of database lock.

    Will the information provided allow FDA to determine if MDCO's classification of clinical presentation is accurate?

    FDA Preliminary Response
    We are uncertain how you determined the "derived-type" is more accurate or even the utility of being "more accurate" for regulatory decision and clinical decision making. The investigators' assessment of clinical presentation as entered in the IVRS at the time of randomization is most likely to reflect the information that a practitioner will have at the time he or she is making the decision about whether to administer cangrelor. Further, investigators were unaware of treatment assignment and the outcomes of PHOENIX when entering clinical presentation whereas you make clear that "derived-type" clinical presentation was determined after study unblinding. The CSR description (section 9.7.1.8.1) of the "derived type" methodology, as well as other documents, failed to discuss key features designed to maintain protocol integrity. Specifically:

    - The SAP is silent on the derivation or use of "derived-type" clinical presentation. We believe that the only pertinent discussion in the SAP is in Section 3.8, which references internal inconsistencies which would be remanded to the Data Manager for further evaluation.
    - Your Data Review Plan adequately described data review tasks (section III) but made no mention about re-classifying entry diagnoses.
    - Your Clinical Data Management Plan described data capture and site personnel resolution of queries based on discrepant data (section IV) but did not describe "derived type" methodology.

Adjunctive Use of Cangrelor in Patients with Stable Angina

15. Does FDA have any comments concerning MDCO's perspective that cangrelor use is supported for PCI patients with stable angina?

    (b) (4)? Is there any other data MDCO can provide?

FDA Preliminary Response

The use of cangrelor at the time of PCI instead of clopidogrel with clopidogrel started only when cangrelor is stopped results in a period of substantially reduced anti-platelet activity from the time cangrelor is discontinued until the time that clopidogrel becomes fully active. We believe it self-evident that avoidance of this period of reduced anti-platelet activity is desirable and can of course be accomplished by administering clopidogrel some hours prior to PCI without need for cangrelor. Patients undergoing PCI for stable symptoms in the absence of ACS can be administered clopidogrel hours before undergoing PCI because there is no urgency to perform the procedure. We will need additional explanations of why it is reasonable to delay clopidogrel's use once PCI is planned.

Relevance of PHOENIX Data to Current American Practice

16. Does FDA have any comments concerning MDCO's perspective that data from PHOENIX are relevant to current American practice?

    If not, what are the implications for labeling? Is there any other data MDCO can provide?

FDA Preliminary Response

While there is no regulatory requirement that the active control in a comparative trial designed to show superiority be best therapy available, the comparator should be reasonably effective and used appropriately as labeled. The most obvious rapidly active effective treatment would have been prasugrel, a drug demonstrated in TRITON to be superior to clopidogrel for prevention of early MIs as well as prevention of stent thrombosis, prasugrel was prohibited although it had been approved for marketing in the USA prior to the initiation of PHOENIX. Apart from not allowing prasugrel, however, control treatment was less than optimal in other ways.

- The use of the most potent and rapid acting anti-platelet drugs available, glycoprotein 2b/3a inhibitors (GPIs), was prohibited except as bailout. We believe that these drugs are not uncommonly used in patients undergoing PCI, especially in patients undergoing PCI during STEMI.
- Administration of clopidogrel at least a few hours prior to PCI increases the anti-platelet effect at the time of PCI because generation of the active metabolite of clopidogrel takes some time. A slide describing when patients in practice were administered clopidogrel relative to PCI was presented at a 2007 Executive Committee meeting for CHAMPION-PCI and PLATFORM. It makes clear that the presenters also believed that "adequate" administration required giving clopidogrel hours before PCI.

We are therefore having difficulty identifying a patient group for whom cangrelor is an appropriate therapeutic choice. We particularly question recommending it for patients with stable angina (see our answer to question # 15).

The implications (b) (4) It seems important for you to explain why you believe that your three studies, particularly in light of the differing outcomes of CHAMPION-PCI CHAMPION-PLATFORM, demonstrate that delaying clopidogrel administration after the start of angioplasty is not harmful to patients.

(b) (4)

Resubmission Requirements, Review, and Timelines

18. Can FDA provide guidance of how the resubmission should be formatted and any additional requirements (i.e., label update) for the resubmission?

FDA Preliminary Response
There are no additional formatting requirements. You should abide by the guidances for industry, "Classifying Resubmissions in Response to Action Letters" and "Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" before resubmission. Please also include all of the required administrative forms with the resubmission (i.e., debarment certification, labeling, etc.). (b) (4) , please include an updated label in the resubmission.

19. Can FDA provide insight into the resubmission review process and timelines?

FDA Preliminary Response
Please see those guidances listed in our preliminary response under Question # 18. Upon receipt of the resubmission of your response to our 30 April 2014 Complete Response Letter, the Agency will meet internally within 14 days to determine if your response constitutes a complete response to all critical aspects of the letter. This decision will be communicated to you within that timeframe. If the resubmission is complete, the application will be reviewed within 6 months of the receipt date of the submission. Please note that it is likely that a second advisory committee (AC) will take place within month 5 of the review cycle.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product

for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. If there are any changes to your development plans between the 30 April 2014 Complete Response Letter and your re-submission that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

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

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/s/

ALISON L BLAUS
08/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

MEETING REQUEST GRANTED

The Medicines Company
ATTENTION: Stephen Sherman, JD, M.B.A.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (cangrelor) for injection.

We also refer to your 20 June 2014 correspondence requesting a meeting to discuss our 30 April 2014 Complete Response (CR) Letter and your resubmission plans aimed to address the letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: 5 August 2014
Time: 0930 – 1100 EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Invited CDER Participants:

* *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
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Nhi Beasley, PharmD	Clinical Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*	
Raj Madabushi, Ph.D.	Team Leader – Clinical Pharmacology
Sudharshan Hariharan, Ph.D.	Acting Team Leader - Clinical Pharmacology
Jeffrey Florian, Ph.D.	Team Leader – Pharmacometrics
Sreedharan Sabarinath, Ph.D.	Reviewer
* *Office of Biostatistics, Biometrics I*	
Jim Hung, Ph.D.	Team Leader
Jialu Zhang, Ph.D.	Statistician
* *Office of Scientific Investigation (OSI), Good Clinical Practices (GCP)*	
Ni Aye, Khin, Ph.D.	Team Leader
Jean Mulinde, M.D.	Reviewer
Susan Thompson, M.D.	Reviewer
Kassa Ayalew	Reviewer
Sharon Gershon, RPh	Reviewer

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

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

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

As soon as possible, please submit the 21 desk copies to the following address:

Alison Blaus
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4158
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

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

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/s/

ALISON L BLAUS
06/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

MEETING MINUTES

The Medicines Company
ATTENTION: Stephen Sherman, JD, M.B.A.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated 30 April 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cangrelor for injection.

We also refer to the meeting between representatives of your firm and the FDA on 4 March 2014. The purpose of the meeting was to discuss the topics raised at the 12 February 2014 Advisory Committee.

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

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Guidance
Meeting Date and Time: 4 March 2014 from 900 – 1000 EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903
Application Number: NDA 204958
Product Name: Kengreal (cangrelor) for injection
Proposed Indication: **PCI**

Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

Bridging

Cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

Applicant Name: The Medicines Company (TMC)
Meeting Chair: Robert Temple, 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
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*	
Madabushi, Rajnikanth, Ph.D.	Clinical PharmacologyTeam Leader
Jeffry Florian, Ph.D.	Pharmacometrics Reviewer
* *Office of Biostatistics*	
Jim Hung, Ph.D.	Director
Jialu Zhang, Ph.D.	Statistician
* *Office of Regulatory Policy*	
Rachel Turow, JD	ORP representative
* *Office of Chief Counsel*	
Donald Beers, JD	OC representative

SPONSOR ATTENDEES

Clive Meanwell, M.D.	CEO
Simona Skerjanec, Pharm.D.	Product Development

Consultants

(b) (4)

(b) (4)

1.0 BACKGROUND

NDA 204958 was submitted on 30 April 2013 and an Advisory Committee (AC) was convened on 12 February 2014 to discuss a number of topics related to this application. This meeting, on 4 March 2014, was scheduled to discuss the issues raised at the AC meeting and whether any new information request would be requested by the Agency in response to those issues.

2. DISCUSSION

- *CHAMPION-PCI and PLATFORM vs. PHOENIX*
  The applicant began the meeting by briefly presenting the results from the PHOENIX trial. The applicant explained that PHOENIX was strengthened by observations from PCI and PLATFORM. The definition of myocardial infarction (MI) used in PHOENIX was changed in that only those MIs that developed in the cardiac catheterization laboratory as a result of the PCI were counted in the PHOENIX trial. The applicant believes that MIs occurring pre-PCI, which are not influenced by cangrelor, may have masked the benefit of cangrelor in the previous CHAMPION trials. Dr. Temple asked what would happen to the results of the trial if all MIs were counted rather than those that occurred only in the cardiac catheterization laboratory. Dr. Temple also asked the applicant to submit a document explaining why the failure of the PCI and PLATFORM trials should not affect our interpretation of the results from the PHOENIX trial. The applicant agreed to provide such a document.
- *Clopidogrel Dose & Timing*
  Dr. Temple asked the applicant to explain the use of two different loading doses of clopidogrel (300 mg or 600 mg) as well as delaying the administration of clopidogrel until after the PCI had begun, rather than providing the same dose of clopidogrel to all subjects prior to PCI. The applicant was also asked to explain why they believe the different clopidogrel loading doses in the PHOENIX trial and the delay in clopidogrel administration relative to PCI would not have affected the primary efficacy results. The applicant cited the data from the fondaparinux OASIS-7 trial that showed clopidogrel 600 mg was not superior to 300 mg for those patients having PCI. The results did show a difference in STEMI patients, however, but this was observed after 48 hours. The applicant argued that timing would not have an impact on the PHOENIX data because the temporal variability of clopidogrel administration was much smaller than the time the patients

spent in the catheterization laboratory. Dr. Temple reiterated that the rationale for allowing variability in both the loading dose and time of clopidogrel administration needs to be addressed in writing and submitted to the FDA.

- *Primary Endpoint for PCI indication*
  The Agency asked the applicant about the definition of intra-procedural stent thrombosis (IPST), one of the components of the primary efficacy endpoint, and how this differs from stent thrombosis (ST). IPST was originally described as occurring when a thrombus is angiographically identified while the stent is being deployed. The adjudication process for IPST was discussed. IPST was defined in the Adjudication Charter as occurring while the patient was still in the catheterization laboratory. In reviewing the start and stop time of PCI captured in the case report forms, the timing of IPST was recorded as occurring precisely at the start of PCI in all the reported cases. The applicant explained that the times reported on the case report forms (CRFs) for IPST were inaccurate but reflected the time the subjects were in the catheterization laboratory. The exact timing of the IPST was not recorded. Dr. Senatore commented that as a consequence of not recording the exact timing of an IPST while the patient was in the catheterization laboratory, it is not clear if the thrombotic event occurred before, during, or after the PCI. Therefore, it is not clear if the diagnosis of IPST is accurate. The applicant acknowledged this and reiterated that in a sensitivity analysis where IPST was removed, the incidence of the primary endpoint was still significantly lower for cangrelor compared to clopidogrel at 48 hours, but not at 30 days. The applicant stated that IPST was a prognostic indicator for cardiac adverse events. Dr. Temple remarked that if a thrombosis occurred in the catheterization laboratory, it should have been treated at that moment. It is not clear that an observed IPST that is resolved while the patient is still in the catheterization laboratory is clinically meaningful. Dr. Temple asked the applicant to submit a document explaining why IPST is important. Dr. Temple also asked the applicant to show the exact timing of the occurrence of an IPST and that it should have been while the stent was deployed but not before. The applicant acknowledged the request and said that they have CRFs to show the time of the IPST.
- *Safety in PHOENIX CHAMPION*
  The higher incidence of GUSTO severe bleeding in subjects treated with cangrelor compared to clopidogrel was discussed. The applicant acknowledged that the Agency found one extra GUSTO severe bleed in the cangrelor arm that was not reported. This was because the applicant used the bleed CRF for their analysis of bleeds, and the investigator did not report this particular event on the bleed CRF. The FDA reviewer found the additional bleed through her search of the serious adverse events.
- *BRIDGE*
  When queried about dose used in BRIDGE compared to the CHAMPION dose, the applicant stated that a population PK/PD model based on several studies (TNC-CAN-05-02-S1, TMC-CAN-05-03-S1, and BRIDGE) suggested a higher dose requirement in the PCI setting. The BRIDGING dose was based on Stage 1 of the BRIDGE protocol. Dr. Temple said that the applicant needs to show how the PK/PD model suggested a higher dose requirement for the CHAMPION setting, and why the data from CHAMPION indicating a clinical effect are relevant to BRIDGE despite the considerably lower dose used in BRIDGE. Dr. Madabushi added that the applicant would also need to consider the difference in patient populations. Dr. Senatore asked the applicant to provide a rationale for requesting a BRIDGE indication in the setting where the exposure to cangrelor for 5 days was based on a sample size too small for a safety evaluation at that exposure duration, and where the clinical outcome data were based on drug administration for less than four hours. The applicant was asked to evaluate the wide variability of PRU values during infusion and post discontinuation and argue why such variation does not pose a safety risk.

- *Bioavailability of Clopidogrel*
  The Agency expressed interest in bioequivalence data of the over-encapsulated clopidogrel. The applicant said they would look into the availability of clinical supplies from PHOENIX.

  Post-Meeting Note
  - In an advice letter dated 9 September 2010, the sponsor was asked to provide a bioequivalence study if they chose to utilize an over-encapsulated clopidogrel in PHOENIX.
  - The sponsor provided comparative dissolution data at 5, 10, 15, 20, 30, and 60 minutes using over-encapsulated Plavix tablets and Plavix tablets with the same composition, sourced from the same US vendors, and manufactured at the same sites as those used in PHOENIX, PCI, and PLATFORM. The applicant also confirmed that they did not have any remaining clinical supply from any of the CHAMPION trials. The dissolution data are under review by the Agency.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no topics discussed at this meeting that warranted a subsequent face-to-face meeting.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Dr. Temple asked the sponsor to submit a document explaining why PCI & PLATFORM failing should have no impact on the interpretation of the PHOENIX trial results. (See *CHAMPION-PCI & PLATFORM vs. PHOENIX* Bullet under Discussion)	The Medicines Company	Sponsor provided a response document to address all of the Agency's requests on 18 March 2014 (SD52)
Information request regarding IPST. (See *Primary Endpoint* bullet under Discussion)	The Medicines Company	Sponsor provided a response document to address all of the Agency's requests on 18 March 2014 (SD52)
BRIDGE Information Request. (See *BRIDGE* bullet under Discussion)	The Medicines Company	Sponsor provided a response document to address all of the Agency's requests on 18 March 2014 (SD52)
Bioavailability Information Request. (See *Bioavailability of Clopidogrel* bullet under Discussion)	The Medicines Company	Sponsor provided a response document to address all of the Agency's requests on 18 March 2014 (SD51)

5.0 ATTACHMENTS AND HANDOUTS

There were no handouts or slide presentations for this meeting.

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/s/

ROBERT TEMPLE
04/14/2014

Blaus, Alison

From: Blaus, Alison
Sent: Friday, April 11, 2014 9:44 AM
To: Stephen Sherman (stephen.sherman@THEMEDCO.com)
Cc: Reg Ops (reg.ops@THEMEDCO.com)
Subject: NDA 204958 - Bleeding Classifications IR

Importance: High

Hi Steve –

In an effort to align the FDA/TMC bleeding classifications and numbers for CHAMPION PHOENIX, we have prepared the attached document. This document explains how the numbers we presented at the 12Feb14 Advisory Committee meeting were reached and how we think they should be presented in labeling.

Please review the attached with your team and submit your response/concurrence to the NDA as soon as possible.

Thank you in advance and please do not hesitate to contact me should you have any questions.
Regards,
Alison

Alison Blaus, RAC
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
p:(301) 796-1138
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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

NDA 204958 – Bleeding Classification Information Request

The purpose of this Information Request is to identify and hopefully resolve the differences between your and our conclusion about the number of GUSTO and TIMI bleeding events in the CHAMPION PHOENIX trial. The difference between your analysis and our analysis was discussed at the recent FDA Advisory Committee meeting. In particular we found differences among the definitions you used for various bleeding scales (see attached Appendix, Table 45 and Table 59 from our clinical review) and the published definitions for classifying bleeding.[1-5] Additionally, we identified more bleeding events using an analysis that identifies bleeds using data from the lab dataset as well as data entered into the bleeding case report form. We believe our analysis results in a more accurate description of the bleeding outcomes in the CHAMPION PHOENIX trial, and so should be used for benefit-risk analysis of the CHAMPION PHOENIX trial and in any label for cangrelor.

Please confirm our analysis of GUSTO and TIMI bleeding event using our approach, which applies the following:

1. We believe that the definitions you used to ascertain the severity of bleeding event differ in some respects from the published definitions of GUSTO and TIMI bleeding events. A clinically overt or overt bleed is defined as an apparent bleed. We are unaware of other definitions. You defined these terms towards the end of the period during which the trial was conducted but before unblinding [Statistical Analysis Plan (SAP) dated 25 October 2012, just shortly before the last patient completed the trial on 14 November 2012], these terms were not defined in the interim SAP dated 18 April 2011, and an investigator checking the box "clinically overt bleed" in isolation did not suffice (see Appendix, Derivation of clinically overt). Your inclusion of many other possible terms to define "clinically overt" or "overt" supports the notion that these terms are ambiguous in the medical community.
2. When classifying severity of bleeding based on change in hemoglobin concentration, we used the Integrated Summary of Safety (ISS) lab dataset (variable LBCHGBLS that adjusts for transfusions from the December 2013 NDA submission) to determine the change in hemoglobin from baseline. We used this approach because hemoglobin and/or hematocrit were often missing or miscalculated on the bleeding CRF. If there was disagreement between the Hg drop noted on the CRF and the ISS lab dataset and a query to the site to resolve the discrepancy was made, then we generally used the resulting information. If there was no query or if the information in the query was not informative, we used the information in the lab dataset because we believe human error was less likely to occur in the lab data set. In your analysis, if the Hg or Hct information was missing from the particular Hg or Hct field of the bleed CRF, you did not attempt to use other sources of information (information found in text boxes of the bleed CRF or the lab dataset). Rather, the event became ineligible to be a TIMI bleed.
3. All subjects whose bleed was not GUSTO severe or GUSTO moderate were classified as GUSTO mild. The 1993 GUSTO paper defined a minor bleed as "other bleeding, not requiring transfusion or causing hemodynamic compromise." The GUSTO mild definition does not appear to have the component "requires intervention", which you added in your final SAP.
4. Non-CABG bleeds were mutually exclusive within each class. There were some subjects with multiple bleed CRFS for what appeared to be one related event. You did not collapse the information from multiple bleed CRFs into one event.

   After careful blinded review of each discrepant case, we now agree with you on five of the cases. Table 1 and Table 2 list the subjects where there remains disagreement between the FDA and The Medicine Company. Please comment on each subject in both tables. The revised summary of bleeding classifications is shown in Table 3.

Table 1. GUSTO classification

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401029051	not reported	severe	Identified from SAE report. Cardiac tamponade and subsequent death.
466001021	mild	moderate	Note in text field of bleed CRF says "Blood transfusion PRC 1 unit".
420009546	moderate and mild	moderate	Three bleed CRFs for what is likely one event. Oozing, access site bleeding required intervention, transfused.
420009554	moderate and mild	moderate	Two bleed CRFs for what is likely one event. Oozing, hematoma ≥ 5 cm, required intervention, led to hospitalization, transfused. Applied worse classification.
420009668	moderate and mild	moderate	Three bleed CRFs filled out. Subject bled and was subsequently transfused. Applied worse classification.

*ISS Hg or Hct refers to the hemoglobin or hematocrit data found in the ISS lab dataset submitted December 2013.

Table 2. TIMI classification

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401012091	not classified	major	Led to hospitalization, prompted evaluation, gastrointestinal, heme positive stool (overt). CRF drop in Hg TIMI major. ISS Hg reduction agrees.
401029051	not classified	major	Identified from SAE report. Subject with cardiac tamponade and subsequent death.
401030062	not classified	major	Hematoma (overt), required intervention, led to hospitalization, transfused. CRF drop in Hg TIMI major. ISS Hg reduction agrees, 5.1 g/dL.
420009546	not classified	major	Oozing, access site bleeding required intervention (overt), transfused. ISS Hg reduction 7.5 g/dL.
449014045	not classified	major	Mallory-Weiss rupture, hematemesis (overt), led to hospitalization. Transfused (after 48 hours from drug start). CRF last Hg within 48 hours from drug start is 9.2 g/dL, thus the reduction from baseline is 8.4 g/dL. ISS lab Hg reduction 5.4 g/dL. The Hg in the dataset was collected prior to the bleed time. Both CRF and lab data indicate a TIMI major bleed.
401010171	not classified	minor	Hematoma (overt). ISS Hg reduction 3.6 g/dL.
401010226	not classified	minor	Hematoma (overt). ISS Hg reduction 3.3 g/dL.

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401010233	not classified	minor	Hematoma, oozing (overt). CRF drop in Hg TIMI minor. ISS Hg reduction 4.9 g/dL.
401011017	not classified	minor	Hematoma, access site bleeding required intervention, led to hospitalization, pseudoaneurysm (overt). Met applicant definition of overt also. CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.1 g/dL.
401028006	not classified	minor	Retroperitoneal bleed (overt), required intervention, prompted evaluation, hemodynamic compromise. Met applicant definition of overt also. ISS Hg reduction 4.6 g/dL.
401029038	not classified	minor	Hematoma (overt). CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.6 g/dL.
401045038	not classified	minor	Hematoma and ecchymosis (overt). ISS Hg reduction 3.3 g/dL.
401045044	not classified	minor	Hematoma ≥ 5 cm, ecchymosis, bleeding from groin site (overt). CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.3 g/dL.
401053021	not classified	minor	Hematoma, oozing (overt). ISS Hg reduction 3.8 g/dL.
401073003	not classified	minor	Oozing, "clinically overt" (overt). ISS Hg reduction 3.0 g/dL.
401079159	not classified	minor	Hematoma ≥ 5 cm (overt). ISS Hg reduction 4.3 g/dL.
401091002	not classified	minor	Oozing, ecchymosis (overt). ISS Hg reduction 3.0 g/dL.
401091428	not classified	minor	Hematoma (overt). ISS Hg reduction 3.0 g/dL.
401091711	not classified	minor	Gastrointestinal, hematemesis, hypotensive with episode, required intervention, led to hospitalization (overt), transfused. CRF drop in Hg blank. Text reports Hg before transfusion, -2.8 g/dL. ISS Hg reduction 4.2 g/dL (accounts for transfusion).
401091761	not classified	minor	Retroperitoneal, hypotensive (overt), transfused. CRF drop in Hg blank. Text reports Hg, TIMI minor. ISS Hg reduction agrees, 3.8 g/dL.
401091767	not classified	minor	Hematoma and ecchymosis (overt). CRF drop in Hg TIMI minor. ISS hg reduction agrees, 3.3 g/dL.
401092008	not classified	minor	Saphenous vein graft perforation required intervention (overt). ISS hg reduction 3.5 g/dL.

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401092029	not classified	minor	Ecchymosis, bloody secretions, "clinically overt",decreased mental status, head CT scan. CRF drop in Hg TIMI minor. ISS hg reduction agrees, 3.5 g/dL.
401097009	not classified	minor	Hematoma ≥ 5 cm (overt), required intervention. ISS Hg reduction 3.7 g/dL.
407005165	not classified	minor	Hematoma ≥ 5 cm (overt). ISS Hg reduction 3.6 g/dL.
407007030	not classified	minor	Hematoma ≥ 5 cm (overt). ISS Hg reduction 3.9 g/dL.
420001073	not classified	minor	Hematoma ≥ 5 cm, "clinically overt", compressive bandage. CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.0 g/dL.
420009209	not classified	minor	Hematoma ≥ 5 cm (overt). CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.9 g/dL.
420009554	not classified	minor	Hematoma ≥ 5 cm, oozing (overt), required intervention, led to hospitalization, transfused. CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 4.7 g/dL.
420009572	not classified	minor	Hematoma ≥ 5 cm, oozing (overt), required intervention, led to hospitalization. CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 3.9 g/dL.
420009801	not classified	minor	Hematoma ≥ 5 cm, oozing (overt), led to hospitalization. ISS Hg reduction 3.2 g/dL.
439009002	not classified	minor	Hematoma ≥ 5 cm (overt). ISS Hg reduction 3.7 g/dL.
448001299	not classified	minor	Hematoma ≥ 5 cm (overt). ISS Hg reduction 3.1 g/dL.
449004014	not classified	minor	Hematoma ≥ 5 cm (overt), led to hospitalization. ISS Hg reduction 3.2 g/dL.
449017024	not classified	minor	Hematoma ≥ 5 cm (overt), access site required intervention. CRF drop in Hg TIMI minor. ISS Hg reduction agrees, 4.9 g/dL.
449017034	not classified	minor	Hematoma ≥ 5 cm, "clinically overt", led to hospitalization. ISS Hg reduction 3.1 g/dL.
455005012	not classified	minor	Ecchymosis (overt), required intervention. ISS Hg reduction 4.1 g/dL.
401007020	minor	not classified	Hematoma ≥ 5 cm (overt), required intervention. CRF drop in Hg TIMI minor (no values provided). ISS Hg reduction disagrees, 0.3 g/dL.

CSUBJECT	Applicant's Classification	FDA's Revised Classification	Reason for FDA classification
401046017	minor	not classified	Hematoma ≥ 5 cm, oozing (overt), required intervention. CRF drop in Hct 9-12% (no values provided). ISS lab reduction disagrees. The closest reported Hct is the next day, Hct reduced by 4.5%. It could be incorrectly calculated as 12.5% (or $\frac{35.8\,\% - 31.3\,\%}{35.8\%} * 100$). Maximum ISS lab reduction Hg 2.2 g/dL, Hct 7.5 %.
401079197	minor	not classified	Hematoma ≥ 5 cm, ecchymosis, required intervention, prompted evaluation, "clinically overt", access site bleeding required intervention, CRF drop in Hct 9 -12% (no values provided). ISS lab reduction disagrees; Hg 1.5 g/dL, Hct 3.0% for the time reported on the bleed CRF.
407005131	minor	not classified	Hematoma ≥ 5 cm (overt), required intervention. CRF drop in Hg 3 to ≤ 4 g/dL. ISS Hg reduction disagrees, 2.2 g/dL for the time reported on the bleed CRF.
459003008	minor	not classified	Genitourinary, "clinically overt", prompted evaluation. CRF drop in Hg 3 to ≤ 4 g/dL. ISS Hg reduction disagrees, 1.9 g/dL for the time reported on the bleed CRF.

*ISS Hg or Hct refers to the hemoglobin or hematocrit data (adjusted for transfusion) found in the ISS lab dataset submitted December 2013. If no "CRF drop in Hg or Hct" noted, then it was missing from the bleed CRF.

Table 3. Non-CABG bleeding classification risk at 48 hours in CHAMPION PHOENIX (revised)

	Cangrelor		Clopidogrel		Cangrelor vs. Clopidogrel		Cangrelor vs. Clopidogrel	
	N=5529	(%)	N=5527	(%)	RR	(95% CI)	OR	(95% CI)
Non CABG bleeds	857[†]	(15.5)	601	(10.9)	1.42	(1.29, 1.56)	1.50	(1.34, 1.67)
GUSTO severe or moderate	32	(0.6)	20	(0.4)	1.57	(0.90, 2.74)	1.57	(0.90, 2.75)
GUSTO severe	10	(0.2)	6	(0.1)	1.64	(0.60, 4.52)	1.64	(0.60, 4.53)
GUSTO severe*	9	(0.2)	6	(0.1)	1.50	(0.53, 4.21)	1.50	(0.53, 4.22)
GUSTO moderate	22	(0.4)	14	(0.3)	1.54	(0.79, 3.00)	1.54	(0.79, 3.01)
GUSTO moderate*	22	(0.4)	13	(0.2)	1.69	(0.85, 3.35)	1.69	(0.85, 3.37)
GUSTO mild	825	(14.9)	581	(10.5)	1.41	(1.28, 1.56)	1.49	(1.33, 1.67)
GUSTO mild*	150	(2.7)	88	(1.6)	1.70	(1.31, 2.21)	1.72	(1.32, 2.25)
TIMI Major or Minor	40	(0.7)	14	(0.3)	2.83	(1.54, 5.19)	2.84	(1.55, 5.23)
TIMI Major	10	(0.2)	5	(0.1)	1.99	(0.68, 5.83)	2.00	(0.68, 5.84)
TIMI Major*	5	(0.1)	5	(0.1)	1.00	(0.29, 3.45)	1.00	(0.29, 3.45)
TIMI Minor	30	(0.5)	9	(0.2)	3.29	(1.56, 6.93)	3.31	(1.57, 6.97)
TIMI Minor*	9	(0.2)	3	(0.1)	3.00	(0.81, 11.07)	3.00	(0.81, 11.10)
Acuity Major	242	(4.4)	143	(2.6)	1.67	(1.36, 2.05)	1.71	(1.39, 2.11)
Barc2	110	(2.0)	66	(1.2)	1.65	(1.22, 2.24)	1.67	(1.22, 2.27)
Barc3a	41	(0.7)	12	(0.2)	3.37	(1.77, 6.40)	3.39	(1.78, 6.45)
Barc3b	16	(0.3)	9	(0.2)	1.74	(0.77, 3.94)	1.74	(0.77, 3.95)
Barc3c	3	(0.1)	1	(0.0)	2.98	(0.31, 28.63)	2.98	(0.31, 28.68)
Bad[‡]	61	(1.1)	41	(0.7)	1.46	(0.99, 2.17)	1.47	(0.99, 2.19)

* Applicant's classification and analysis

[†] Reviewer identified an extra bleed (CSUBJECT 401029051) based on SAE report (no BLD CRF page so subject was excluded from Applicant's report). Classified as GUSTO severe, TIMI major and BARC 3b.

[‡] Bad defined as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization

Reviewer's analysis with factors patient status, gender. Reviewer code: bleed\postAC\primary safety ptstatus gender final. Datasets: raw\bld, iss\fda_bld, iss lab.

Appendix

Table 45. Differences between bleed definitions/what was used for classification

Term	What was used for classification
Clinically overt or overt bleeding	The reviewer defined this as any sign of bleeding (including bleeding seen on imaging). This differs from the Applicant's definition which attempted to assign a severity (see Table 4). This likely affected the counts for TIMI, ACUITY, and BARC.
Drop in hemoglobin or hematocrit	The reviewer noted that this field was sometimes incorrectly marked or not marked on the eCRF, so the reviewer used the ISS lab dataset to obtain the adjusted Hg data for all definitions (TIMI, ACUITY, and BARC) that included a drop in hemoglobin. The Applicant used the field as marked in the eCRF.
BARC	Part of the definition includes a Hg drop of < 5 g/dL and ≥ 5 g/dL. The reviewer and the Applicant used ≤ 5 g/dL and > 5 g/dL.
Intervention	If the investigator took action to stop the bleed, then the reviewer marked it as an intervention. This might have contributed to differences between the reviewer's and Applicant's BARC3b and ACUITY major.
GUSTO mild	The reviewer classified all bleeds that were not GUSTO severe or moderate as mild. The Applicant required that at least one of the following on the CRF also be marked: requiring intervention… leading to hospitalization… prompting evaluation… access site bleeding…

Table 59. Non CABG Bleeding Classification Risk at 48 hours in PHOENIX

	Cangrelor		Clopidogrel		Cangrelor vs. Clopidogrel		Cangrelor vs. Clopidogrel	
	N=5529	(%)	N=5527	(%)	RR	(95% CI)	OR	(95% CI)
Non CABG bleeds	857†	(15.5)	601	(10.9)	1.42	(1.29, 1.56)	1.50	(1.34, 1.67)
GUSTO severe or moderate	32	(0.6)	20	(0.4)	1.57	(0.90, 2.74)	1.57	(0.90, 2.75)
GUSTO severe	10	(0.2)	6	(0.1)	1.64	(0.60, 4.52)	1.64	(0.60, 4.53)
GUSTO severe*	9	(0.2)	6	(0.1)	1.50	(0.53, 4.21)	1.50	(0.53, 4.22)
GUSTO moderate	22	(0.4)	14	(0.6)	1.54	(0.79, 3.00)	1.54	(0.79, 3.01)
GUSTO moderate*	22	(0.4)	13	(0.2)	1.69	(0.85, 3.35)	1.69	(0.85, 3.37)
GUSTO mild	825	(14.9)	581	(10.5)	1.41	(1.28, 1.56)	1.49	(1.33, 1.67)
GUSTO mild*	150	(2.7)	88	(1.6)	1.70	(1.31, 2.21)	1.72	(1.32, 2.25)
TIMI Major or Minor	38	(0.7)	12	(0.2)	3.14	(1.64, 6.00)	3.15	(1.65, 6.04)
TIMI Major	9	(0.2)	3	(0.1)	3.00	(0.81, 11.09)	3.01	(0.81, 11.11)
TIMI Major*	5	(0.1)	5	(0.1)	1.00	(0.29, 3.45)	1.00	(0.29, 3.45)
TIMI Minor	29	(0.5)	9	(0.2)	3.18	(1.51, 6.71)	3.19	(1.51, 6.75)
TIMI Minor*	9	(0.2)	3	(0.1)	3.00	(0.81, 11.07)	3.00	(0.81, 11.10)
Acuity Major	242	(4.4)	143	(2.6)	1.67	(1.36, 2.05)	1.71	(1.39, 2.11)
Barc2	111	(2.0)	66	(1.2)	1.67	(1.23, 2.26)	1.68	(1.24, 2.29)
Barc3a	41	(0.7)	14	(0.3)	2.88	(1.57, 5.27)	2.90	(1.58, 5.32)
Barc3b	15	(0.3)	7	(0.1)	2.11	(0.86, 5.16)	2.11	(0.86, 5.18)
Barc3c	3	(0.1)	1	(0.0)	2.98	(0.31, 28.63)	2.98	(0.31, 28.68)
Bad‡	61	(1.1)	41	(0.7)	1.46	(0.99, 2.17)	1.47	(0.99, 2.19)

* Applicant's classification and analysis
† Reviewer identified an extra bleed (CSUBJECT 401029051) based on SAE report (no BLD CRF page so subject was excluded from Applicant's report). Classified as GUSTO severe, TIMI major and BARC 3b.
‡ Bad defined as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization
Reviewer's analysis with factors patient status, gender. Reviewer code: bleed\primary safety ptstatus gender final. Datasets: raw\bld, iss\fda_bld, iss lab.

Derived definition of clinically overt or overt source of bleed from the SAP 25 October 2012

Definition of "clinically overt" bleed: The definition for "clinically overt" or "overt source of" bleeding utilized in all of the bleeding scale definitions should include:

At least one of the following on the eCRF must be checked:

- Requiring intervention: health care professional-guided medical treatment or percutaneous intervention
- Leading to hospitalization or an increased level of care: prolonged hospitalization or hospital transfer
- Prompting evaluation: an unscheduled visit to healthcare professional resulting in diagnostic testing

AND any of the following on the eCRF is checked:

- Clinically overt bleed
- Intracranial hemorrhage
- Intraocular
- Cardiac tamponade
- Retroperitoneal
- Access site bleeding requiring radiologic or surgical intervention
- Reoperation for bleeding
- Hemodynamic compromise
- Epistaxis
- Gross hematuria
- Hematemesis
- Hematoma >= 5 cm at puncture site

References

1. Antman EM, Morrow DA, McCabe CH et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). Am Heart J. 2005;149(2):217-226.

2. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Eng J Med. 1993;329:673-682.

3. Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials, A consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-2747.

4. Stone GW, Bertrand M, Colombo A et al. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: study design and rationale. Am Heart J. 2004;148:764–775.

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/s/

ALISON L BLAUS
04/11/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204958

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

ATTENTION: Stephen Sherman
Senior Director of Global Regulatory Affairs

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated and received April 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cangrelor for Injection, 50 mg per vial.

We also refer to:

- your correspondence, dated and received January 14, 2014, requesting review of your proposed proprietary name, (b) (4)
- your amendment, dated and received January 16, 2014, clarifying the spelling of the proposed proprietary name, Kengreal

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

If **any** of the proposed product characteristics as stated in your January 14, 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 Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. 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/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/29/2014

Blaus, Alison

From: Blaus, Alison
Sent: Monday, March 24, 2014 11:46 AM
To: Stephen Sherman (stephen.sherman@THEMEDCO.com)
Cc: Reg Ops (reg.ops@THEMEDCO.com)
Subject: NDA 204958 - Clinical Information Request

Importance: High

Hi Steve –

In response to your submission dated 19March2014 and your email from the same date, we had a follow-up clarification and question.

1. As part of the 12Mar14 email/information request, we asked the following question:
   2F - Please provide cross-tabulations of primary endpoint rates by treatment arm and IVRS patient type and by treatment arm and your derived "baseline" patient type.

MDCO Response (from your 19Mar14 response):
We are puzzled by this question. The "derived patient type" is the baseline patient type. As discussed above, it was the result of applying an algorithm to baseline data provided by the sites. Thus, there is no comparison to be made.

FDA Response

To clarify, please provide cross-tabulations of primary endpoint rates by treatment arm and IVRS patient type and by treatment arm and your derived "baseline" patient type. IVRS patient type is the PTTYPE variable in your DEM dataset and on the demographics CRF (with the latter indicating it was

imported from the IVRS). Please contact me to discuss if you are still puzzled by this request.

2. In your email dated 19Mar14 you confirmed that the slide [from the January 2013 Executive Committee update) stating that (b) (4) of PHOENIX sites were CHAMPION sites was wrong and the dataset USIT141.XPT, in which about 54% of the PHOENIX sites are also CHAMPION sites, from your March 5 submission is correct.

We compared site names among the three trials and believe that the following PHOENIX sites may also be PLATFORM sites:

usite	csitenam
459002	mhat 'tokuda hospital sofia', ad
455002	hospital felicio rocho
420002	fakultni nemocnice hradec kralove [university hospital]
455017	hospital s?o jose
420008	mestska nemocnice ostrava [ostrava city hospital]

In addition, the following PHOENIX sites may also be PCI sites:

usite	
495003	
csitenam	
eopl. tbilisi state medical university-alexandre aladashvili university clinic	

usite	
455002	
csitenam	
hospital felicio rocho	

usite	
443005	
csitenam	
landeskrankenhaus feldkirch	

Both tables include sites that were not included in LSIT141.XPT but were in USITEIDS.XPT from your 24 February 2014 submission.

a) Please confirm whether the above listed sites are PCI or PLATFORM sites.

b) If checking these sites confirms that there were sites misclassifed in either submission, please check all sites and submit an updated USITEIDS.XPT.

c) Please state your verified count of how many PHOENIX sites were also PCI or PLATFORM sites.

****Please retain this email as documentation of this request****

If you have any questions, please let me know. So that we can maintain our timelines, a response by **31Mar14** would be much appreciated.
Thank you in advance –
Alison

Alison Blaus, RAC
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
p:(301) 796-1138
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Address for desk and courtesy copies:
Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4158
Silver Spring, MD 20993

Address for official submissions to your administrative file:
Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

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/s/

ALISON L BLAUS
03/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

GENERAL ADVICE

The Medicines Company
ATTENTION: Stephen Sherman, JD, M.B.A.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

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

We also refer to your 27 February 2014, submission, containing a revised presentation of the carton and container labeling for Kengreal.

Container Label

1. Please revise the order of the product information. The customary order of information should be: proprietary name followed underneath by the full established name, followed underneath by strength; see example below:

   Kengreal
   (cangrelor) for injection
   50 mg per vial

2. Please revise the font size of the dosage form to match the font size of the active ingredient because the dosage form is part of the established name and should be consistent.
3. Please revise the storage condition statement on the side panel to correspond with the storage condition statement in the insert labeling.
4. Add the statement "Must be reconstituted and diluted prior to use" on the principal display panel to highlight these important steps.
5. Remove the (b) (4) statement at the end of the ingredient list. This information is redundant and already presented on the principal display panel.
6. Add the 'Rx Only' statement to the principal display panel per 21 CFR 201.100.
7. Add the usual dosage statement per 21 CFR 201.55 as exhibited in the example below:

   "**Usual Dose:** See package insert for dosage information."

Carton Labeling

1. Please apply comments 1-6 noted above to the carton labeling.
2. Please ensure the net quantity statement appears in an area of the principal display panel that is away from the product strength and with less prominence to decrease confusion.
3. Please move the UPC barcode to the side panel to decrease clutter on the principal display panel.

4. Remove the [redacted] (b) (4) from the principal display panel. This information is customarily provided on the back panel.
5. Revise the reconstitution instructions to read '**Reconstitution:** Add 5 mL of Sterile Water..."
6. Revise the usual dosage statement to read '**Usual Dose:** See package insert for dosing information'.

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/

ALISON L BLAUS
03/21/2014

NORMAN L STOCKBRIDGE
03/21/2014

Blaus, Alison

From: Blaus, Alison
Sent: Wednesday, March 12, 2014 10:43 AM
To: Stephen Sherman (stephen.sherman@THEMEDCO.com)
Cc: Reg Ops (reg.ops@THEMEDCO.com)
Subject: NDA 204958 - Clinical Information Request

Importance: High

Hi Steve

We had an internal meeting after our 4Mar14 Post-AC meeting with The Medicine's Company and have a few more outstanding questions that we would like answered. Responses to these will help in completing our primary review addendums.

1. The protocol states that "stratification based on site, baseline status as defined by a combination of biomarkers and symptoms, as well as by intended clopidogrel loading dose" while the CSR states that ""Patient randomization was stratified by patient type (SA, NSTE-ACS, STEMI), planned clopidogrel loading dose in the clopidogrel treatment arm (600 mg or 300 mg), and patient baseline status (normal ischemic status, abnormal ischemic status) among other factors."
    a. Please clarify how randomization was stratified.
    b. Please explain "among other factors".
    c. Please submit an updated version of RAND.xpt including a record for all randomization numbers generated with block number, sequence number within the block, and stratification factors. Include a DEFINE.PDF file with more detailed explanations of the variables. For time variables please indicate the time zone. If the randomization times have not been standardized to one time zone, please generate and submit a standardized randomization time variable.

2. The CEC Charter specifies that the CEC was to confirm baseline STEMIs and was not to adjudicate MI endpoints if baseline STEMI. The SAP describes a potential subgroup analysis as "Diagnosis/Patient Type: STEMI, Not STEMI (SA and NSTE-ACS)." The CSR states that "Patient type was reported as determined by the site investigators at the time of randomization, and as programmatically derived from patient data collected in the CRF. Data provided by the site investigators at the time of randomization via the IV/WRS was limited by the amount of clinical information available at the time and could not be updated within the IV/WRS by system design, even when more data became available. For this reason, programmatic assessment of patient type using the data in the eCRF was used in all efficacy and safety analyses."
    a. Please provide the program to generate derived patient type.
    b. Please justify why analyses of patient type using non-baseline data, i.e., "when more data became available", are appropriate.
    c. Please explain the deviation from the SAP, i.e., the CSR uses the tripartite patient type rather than the bivariate specified in the SAP.
    d. In your derived patient type STEMI subgroup 18 patients had adjudicated MIs. Did you check your derived patient type against the CEC adjudication of baseline STEMI?
    e. Please justify the assignments of STEMI and of MI event for the 18 patients with derived patient type STEMI and adjudicated MIs.
    f. Please provide cross-tabulations of primary endpoint rates by treatment arm and baseline patient type and by treatment arm and your derived patient type.

A response to the above should be separate from the document you are preparing as a result of the 4Mar14 meeting. Please retain this email as formal documentation of this request.

****Please confirm receipt via email****

Once you have had a chance to discuss the above with your team, please provide a ballpark submission date for your response.
Thank you in advance!
Alison

Alison Blaus, RAC
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
p:(301) 796-1138
f:(301) 796-9838

Address for desk and courtesy copies:
Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4158
Silver Spring, MD 20993

Address for official submissions to your administrative file:
Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

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/s/

ALISON L BLAUS
03/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

MEETING REQUEST GRANTED

The Medicines Company
ATTENTION: Stephen Sherman, JD, M.B.A.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

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

We also refer to your 21 February 2014, correspondence requesting a meeting to discuss the topics raised at the 12 February 2014 Advisory Committee. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: 4 March 2014
Time: 900 – 1000 EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Invited CDER Participants:

* *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
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Nhi Beasley, PharmD	Clinical Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Health Project Manager
* *Office of Clinical Pharmacology*	
Madabushi, Rajnikanth, Ph.D.	Team Leader
Sreedharan Sabarinath, Ph.D.	Reviewer
* *Office of Biostatistics*	
Jim Hung, Ph.D.	Director
Jialu Zhang, Ph.D.	Statistician

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

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

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/s/

ALISON L BLAUS
02/24/2014

From:	Stephen Sherman
To:	Bengtson, Karen
Cc:	Milburn, Cherye; Reg Ops
Subject:	RE: NDA 204598 Cangrelor for Injection - Request for Proprietary Name Review
Date:	Wednesday, January 15, 2014 10:15:47 AM

Thank you, will do.

Steve Sherman
Senior Director, Global Regulatory Affairs

THE MEDICINES COMPANY®
8 Sylvan Way
Parsippany, NJ 07054
E-MAIL: stephen.sherman@TheMedCo.com
PHONE: (973)-290-6300

From: Bengtson, Karen [mailto:Karen.Bengtson@fda.hhs.gov]
Sent: Wednesday, January 15, 2014 10:15 AM
To: Stephen Sherman
Cc: Milburn, Cherye; Reg Ops
Subject: RE: NDA 204598 Cangrelor for Injection - Request for Proprietary Name Review

Dear Mr. Sherman,

Thank you for the quick response. Please note that you do not need to resubmit the entire proprietary name request, only an amendment with the clarification. Please make sure that the cover letter includes the header "Amendment to Request for Proprietary Name Review."

Regards,
Karen

From: Stephen Sherman [mailto:stephen.sherman@THEMEDCO.com]
Sent: Wednesday, January 15, 2014 10:02 AM
To: Bengtson, Karen
Cc: Milburn, Cherye; Reg Ops
Subject: RE: NDA 204598 Cangrelor for Injection - Request for Proprietary Name Review

Dear Ms. Bengtson,

I apologize for the confusion, we are re-submitting the proprietary name request with the correct name, Kengreal.

Best regards,
Steve Sherman
Senior Director, Global Regulatory Affairs

THE MEDICINES COMPANY®
8 Sylvan Way

Parsippany, NJ 07054
E-MAIL: stephen.sherman@TheMedCo.com
PHONE: (973)-290-6300

From: Bengtson, Karen [mailto:Karen.Bengtson@fda.hhs.gov]
Sent: Wednesday, January 15, 2014 9:30 AM
To: Stephen Sherman
Cc: Milburn, Cherye
Subject: NDA 204598 Cangrelor for Injection - Request for Proprietary Name Review
Importance: High

Dear Mr. Sherman,

Please refer to your submission dated 1/14/14 containing your Request for Proprietary Name Review. We request that you clarify the spelling of your proposed proprietary name. The cover letter shows the proposed name as (b) (4) however, the draft carton and container labeling submitted shows the proprietary name as (b) (4)

Please submit an amendment to the Request for Proprietary name review with the correct spelling and cite the original 1/14/14 submission and eCTD sequence # by COB Tuesday, January 21, 2014.

Please acknowledge receipt of this email correspondence.

Kind regards,
Karen (on behalf of Cherye Milburn, OSE Safety Regulatory Project Manager)

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

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/s/

KAREN E BENGTSON
01/23/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204958

PROPRIETARY NAME REQUEST
UNACCEPTABLE

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

ATTENTION: Stephen Sherman
Senior Director, Global Regulatory Affairs

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated and received April 30, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cangrelor for Injection, 50 mg per vial.

We also refer to your correspondence dated October 10, 2013, received October 11, 2013, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

1. (b) (4)

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

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. 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/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/08/2014

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 Non Responsive
11:10

NDA 204958 (b) (4) (cangrelor) Full Waiver

Non Responsive

Non Responsive

Non Responsive

(b) (4) (cangrelor) Full Waiver

- NDA 204958 seeks marketing approval for (b) (4) (cangrelor) for (1) reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), and (2) maintenance of $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS), or patients with stents, who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.
- The application has a PDUFA goal date of April 30, 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.

Non Responsive

Non Responsive

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/s/

JANE E INGLESE
12/02/2013

From:	Knight, Yvonne
To:	stephen.sherman@themedco.com
Cc:	Knight, Yvonne
Subject:	Information Request for NDA 204958 (Prompt Response)
Date:	Monday, November 25, 2013 5:41:28 PM
Importance:	High

Good Afternoon Mr. Sherman,

We have the following information request concerning The Medicines Company Inc. New Drug Application (NDA) NDA 204958. We request a prompt response to this IR request **before Monday December 9, 2013**.

1. Provide updated drug substance specification with (b) (4) assay limit and the quantitative sodium test and acceptance criterion. Details of the quantitative sodium test method and justification for its acceptance criterion can be submitted to the NDA or to DMF (b) (4) before 9 DEC 2013.
2. Provide updated drug product specification which includes the (b) (4) reconstitution time limit.

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

Best Regards,

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

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/s/

YVONNE L KNIGHT
11/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

MID-CYCLE COMMUNICATION

The Medicines Company
ATTENTION: Stephen Sherman, Ph.D.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Sherman:

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

We also refer to the teleconference between representatives of your firm and the FDA on 21 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.
Team Leader, Clinical
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: 21 October 2013 from 1330 to 1430
Application Number: NDA 204958
Product Name: cangrelor injection
Proposed Indication: **PCI**

Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

Bridging

Cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

Applicant Name: The Medicines Company
Meeting Chair: Thomas Marciniak, M.D.
Meeting Recorder: Alison Blaus, RAC

FDA ATTENDEES

* *Office of Drug Evaluation I*	
Colleen Locicero	ADRA
* *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
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Nhi Beasley, PharmD	Clinical Reviewer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology/Toxicology
Belay Tesfamariam, Ph.D.	Pharmacology/Toxicology Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D	Team Leader
Sreedharan Sabarinath, Ph.D.	Reviewer
* *Office of Biostatistics*	
Jialu Zhang, Ph.D.	Statistician
**Office of New Drug Quality Assessment*	
David Claffey, Ph.D.	Reviewer
* *Office of Surveillance and Epidemiology*	
Reema Mehta, PharmD	DRISK Team Leader
Somya Dunn, M.D.	DRISK Reviewer
* *Office of Biostatistics*	
Jialu Zhang, Ph.D.	Statistician

THE MEDICINES COMPANY ATTENDEES

Jayne Prats, Ph.D.	Clinical Pharmacology
Jonathan Day, M.D., Ph.D.	Medical Director
Meredith Todd	Program Management
Simona Skerjanec, PharmD	Product Development
Stephen Sherman, JD, MBA	Global Regulatory Affairs
Tiepu Liu, M.D., Ph.D.	Senior Director, Biostatistics
(b) (4)	
Brad Zerler	Preclinical Safety
(b) (4)	

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

- David Claffey had no significant review issues to highlight at this point, but noted that he was waiting for the applicant's response to their 18 October 2013 information request letter.

Post-Meeting Note
Microbiology had the following labeling comments that should be provided to the applicant:

The conclusions of the growth promotion study of the reconstituted and diluted product, submitted on 9 October 2013, are not reflected in product labeling. Product labeling indicates that the drug product diluted in either 5% Dextrose or 0.9% Sodium Chloride Injection may be stored at room temperature for [redacted] (b) (4) The suggested storage period for product diluted in Sodium Chloride for Injection, at 24 hours, is supported by the study and is acceptable. Please [redacted] (b) (4) the product labeling [redacted] (b) (4) the storage period for the reconstituted drug product, diluted in 5% Dextrose to 12 hours at room temperature.

Pharmacology & Toxicology

- Dr. Tesfamariam noted that based on impairment of fertility and adverse embryo-fetal development in animal studies, the labeling for cangrelor should recommend that pregnant women not be administered cangrelor. The proposed language will be provided at the time of labeling negotiations.

Clinical Pharmacology

- Dr. Sabarinath asked the sponsor to provide a correlation between the PRU from VerifyNow P2Y12 assay utilized in BRIDGE study and inhibition in platelet aggregation as measured using Light Transmission Aggregometry (LTA) with 20 µMol ADP as agonist.

Clinical

- <u>BRIDGE</u>
  - Dr. Senatore explained that the evidence supporting PRU as a prognostic indicator of adverse events was not strong. From Breet, L, et al (2010), there was no evidence that on treatment PRU cut points with risk for periprocedural events are the same as those associated with long-term risk. From the GRAVITAS trial, there was no correlation between PRU and clinical outcome. Regarding the risk of thrombotic events from terminating clopidogrel too early, the Dutch Stent Registry adequately demonstrated that cessation of clopidogrel therapy, especially less than 30 days post stent placement and in the absence of aspirin, was a strong predictor of stent thrombosis, where the mean follow-up time was 30.9 months (25^{th} percentile 23.6 months, 75^{th} percentile 41.9 months). However, the sponsor did not adequately demonstrate that the results from the Dutch Stent Registry are applicable to the Bridging scenario. Regarding the risk of bleeding from continued use of clopidogrel too close to surgery, the supportive data was contradictory (Biancari, F, et al., 2012), based upon small retrospective subgroup analyses which scored poorly on bias analysis (Nijjer, S, et al., 2011), and in alignment with the current guideline to discontinue clopidogrel 5 days prior to CABG (Au, A, et al., 2012). In the latter study, despite the authors' acknowledgement of significant weaknesses inherent in the analysis, the results showed that exposure to clopidogrel within 5 days prior to CABG empirically increased the risk of stroke, re-operation for bleeding, and all—cause mortality up to 30 days post-surgery. While this specific finding appears to support the sponsor's program hypothesis, there was no evidence offered by the sponsor that cangrelor exposure up to the day of CABG would not result in similar adverse events 30 days post-surgery.

- <u>Bleeding</u>
  - Dr. Beasley noted that bleeding was not adjudicated. She explained that she was using various definitions and criteria to analyze the bleeding data. There appeared to be differences between her review and the applicant's assertions of bleeding risk. Dr. Marciniak said that this is a risk vs. benefit issue for both indications and begs the question as to whether

the applicant chose the correct dose. Both Dr. Beasley and Marciniak invited the sponsor to provide additional analyses if they could further support their assertions.

- Post-procedural Follow-up
  - Dr. Beasley noted that with the exception of the primary efficacy endpoints, there appeared to be no systematic collection of safety data beyond 48 hours after treatment initiation. There also appeared to be discrepancies between the clinical study report and the data. It would have been helpful to capture safety data beyond 48 hours. She noted that there was a large difference between the rate of MI within 48 hours and from 48 hours to 30 days.

- Comparator use
  - *Timing of Clopidogrel*
    Dr. Marciniak said that in three studies (CHAMPION-PCI, CHAMPION-PLATFORM, & PHOENIX), it seemed the later clopidogrel was administered, the better cangrelor looked (and vice versa). He added that the administration of clopidogrel did not seem per EU guidelines and its use seemed to be unethical.

  - *Choice of Comparator*
    Dr. Marciniak noted that there was virtually no data vs. the newer, more effective, agents (i.e., prasugrel, ticagrelor, etc.). He also explained that he was not sure there was any benefit of cangrelor when a glycoprotein IIb/IIIa was used.

- Event rate
  - Dr. Marciniak said that it was interesting to note that the overall event rate in PHOENIX was much lower than other trials conducted in the patient population (i.e., rivaroxaban's Phase 3 ATLAS). With that said, the clinical team will be reviewing the definition of myocardial infarction (MI) used in the trial and not just the CEC adjudicated cases of MI.

Biostatistics

- Dr. Zhang said that she had no significant review issues with the application at this point in time.

3.0 INFORMATION REQUESTS

At the time of the mid-cycle communication meeting there were six outstanding CMC information requests. All six requests were included in Information Request letter dated 18 October 2013.

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 the Somya Dunn 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 the remainder of the review process.

5.0 ADVISORY COMMITTEE MEETING

As mentioned in our 12 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:

AC Alignment Meeting: 16 December 2013
Advisory Committee Meeting Book Due (Medicines Company): 10 January 2014
Advisory Committee Meeting Book Due (FDA): 15 January 2014
FDA Slides Due: 10 February 2014
AC: 12 February 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): 17 January 2014
Late Cycle Meeting Briefing Book Due to Medicines Company: 21 January 2014
Late-Cycle Meeting w/Sponsor: 29 January 2014

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/s/

ALISON L BLAUS
11/13/2013

THOMAS A MARCINIAK
11/13/2013

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

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

NDA#: 204958

PRODUCT PROPRIETARY NAME: (b) (4) **ESTABLISHED/GENERIC NAME: cangrelor**

APPLICANT: The Medicines Company

PREVIOUSLY APPROVED INDICATION/S:
(1) _none_____

PROPOSED INDICATION/S:
(1) **PCI**

(b) (4) (cangrelor for injection) is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, (b) (4) significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

(2) **Bridging**

(b) (4) (cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

NDA STAMP DATE: 30 April 2013
PDUFA GOAL DATE: 30 April 2014
SUPPLEMENT TYPE: NME NDA
SUPPLEMENT NUMBER: n/a

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

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

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

Yes ☐ ***No*** ☒

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

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

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

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

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

WAIVER REQUEST

Please attach:

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

☒ ***Pediatric Record***

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

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

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

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

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

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

3. *Provide justification for Waiver:*

Coronary artery disease is extremely rare in the pediatric population. Waiver is supported by the highlighted information in the table below.

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

We agree with the sponsor's proposed language which is consistent with 21 CFR 201.57 - "Safety and effectiveness in pediatric patients have not been established".

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

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

Age-related macular degeneration	Cancer:
Alzheimer's disease	Basal cell
Amyotrophic lateral sclerosis	Bladder
Atherosclerotic cardiovascular disease	Breast
Benign Prostatic Hyperplasia	Cervical
Chronic Obstructive Pulmonary Disease	Colorectal
Erectile Dysfunction	Endometrial
Infertility	Gastric
Menopausal and perimenopausal disorders	Hairy cell leukemia
Organic amnesic syndrome	Lung (small & non-small cell)
(not caused by alcohol or other psychoactive substances)	Multiple myeloma
Osteoarthritis	Oropharynx (squamous cell)
Parkinson's disease	Ovarian (non-germ cell)
Postmenopausal Osteoporosis	Pancreatic
Vascular dementia/ Vascular cognitive disorder/impairment	Prostate
Actinic Keratosis	Renal cell
	Uterine

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

INFORMATION REQUEST

The Medicines Company
Attention: Stephen Sherman, Sr. Director
Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

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

We also refer to your April 30, 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.

1. Regarding the stability of the reconstituted cangrelor solutions we note that the 2010 report concluded that "the stability for the (b) (4) mg/ml Cangrelor solutions could not be determined with any confidence from these data". We also note that in a similar 2006 study reported failures in assay due to "possibly a sampling issue or assay variability" and related substances due to "handling/storage of the samples and/or possibly analytical technique". These studies were repeated until the results were found acceptable without determining the cause of these failures. Given that both of these studies aimed to demonstrate drug product quality prior to administration, we request that additional data be provided (using aged samples with validated methods) that unequivocally demonstrate that the reconstituted drug product is of acceptable quality through the proposed hold period.

2. Amend the drug product specification to include a single acceptance criterion for total degradants, e.g. (b) (4)%. The other acceptance criterion can be used as part of your internal control strategy.

3. We request that the drug product acceptance criterion for reconstitution time be (b) (4) to be more in line with recent drug product batches e.g. (b) (4) (b) (4)

[redacted] (b) (4)

4. Include a quantitative test for sodium to the drug substance specification as there are no other tests in place to ensure that the drug substance is a tetrasodium salt.

5. Provide all available updated drug product stability data.

6. Considering that drug substance quality depends greatly on release testing and that recent lots generally had assay results > [redacted] (b) (4) (b) (4)

Your application referenced the Drug Master File (DMF) [redacted] (b) (4) This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on October 18, 2013.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

OLEN M STEPHENS
10/18/2013

For Internal Use Only

Meeting Request Withdrawal Form

Application Type	NDA
Application Number	204958
DATE Meeting Withdrawn (per communication with requester)	7 October 2013
Scheduled Meeting Date	n/a
Reason Meeting Withdrawn	This Type C pediatrics meeting request was withdrawn by the sponsor from the pending NDA 204958. The conversation related to (b) (4) would be more appropriate under (b) (4). No preliminary responses were provided and no meetings were scheduled in response to the request.
Project Manager	Alison Blaus

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/s/

ALISON L BLAUS
10/09/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204958

PROPRIETARY NAME REQUEST
UNACCEPTABLE

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

ATTENTION: Stephen Sherman
Senior Director, Global Regulatory Affairs

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA), dated and received April 30, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cangrelor for Injection, 50 mg per vial.

We also refer to your correspondence dated and received August 9, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i); (e)(6)(i)].

We note that you have proposed an alternate proprietary name in your submission dated August 8, 2013. In order to initiate the review of the alternate proprietary name (b) (4), submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye 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, (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/

CAROL A HOLQUIST
10/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204958

PROPRIETARY NAME REQUEST
UNACCEPTABLE

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

ATTENTION: Stephen Sherman
Senior Director, Global Regulatory Affairs

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA), dated and received April 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cangrelor for Injection, 50 mg per vial.

We also refer to your correspondence dated and received May 2, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, the new proprietary name should not include a modifier. We recommend that you submit a new request for a proposed proprietary name review (see the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012").

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye 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/

CAROL A HOLQUIST
07/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

FILING COMMUNICATION

The Medicines Company
ATTENTION: Stephen Sherman, Ph.D.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Sherman:

Please refer to your New Drug Application (NDA) dated April 30, 2013, received April 30, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for cangrelor for injection.

We also refer to your amendments dated May 2, 6, 15, 23 and June 22 and 25, 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 **April 30, 2014**.

Your NDA does not qualify for a priority review because effectiveness was not established against best available therapy.

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 17, 2014.** In addition, the planned date for our internal mid-cycle review meeting is **October 7, 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. The Clinical Events Committee (CEC) Charter, finalized on 18 SEP 2011, described incorporation of the secondary endpoint intra-procedural stent thrombosis (IPST) into the ARC-defined stent thrombosis (ST) which is a component of the composite primary endpoint. The protocol, amended on 28 SEP 2010, introduced IPST as a secondary endpoint distinct from ST. The SAP, finalized on 25 OCT 2012, described the hierarchical efficacy evaluation process whereby IPST was specified as a secondary endpoint, distinct from ST, in alignment with the amended protocol. This action by the CEC appeared to be independent of the protocol and was without further protocol amendment. The misalignment of the CEC Charter-defined primary endpoint and the protocol-defined primary endpoint might require re-adjustment of the comparison between the cangrelor arm and the clopidogrel arm. We acknowledge that you have already conducted an analysis of the composite primary endpoint results without IPST.

2. The Angiographic Core Laboratory Charter of the Cardiovascular Research Institute detailed the description of pre- and post-stent deployment angiographic parameter analysis, but did not define how IPST was evaluated. The distinction between IPST and ARC-defined acute stent thrombosis is not clear in the Angiographic Core Laboratory Charter.

3. ARC-ST was defined angiographically with accompanying clinical signs or symptoms. IPST was defined angiographically without accompanying clinical signs or symptoms. We acknowledge, based on published studies of IPST, that there are significant associations between IPST and baseline parameters (e.g., STEMI, TIMI-flow, bifurcation lesions, type of stent deployment), and between IPST and clinical outcome (e.g., MACE, ARC-ST, TIMI-major bleed). We could not readily demonstrate these significant associations upon initial review of the PHOENIX data, thereby raising the question of whether or not IPST as reported from PHEONIX is clinically relevant.

4. It is not clear how the most recent inter-reader variability analysis of IPST (kappa 0.7125) impacted the statistical significance of this parameter.

5. Universal Definition of MI type 4a (associated with PCI) was significant in favor of cangrelor, but type 4b (associated with ST) was not significantly different between the two arms. It is not clear why a positive result with ST as a key driver of the composite primary endpoint was not accompanied by a corresponding result with MI associated with ST.

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. Microbiological data should be provided to demonstrate that the reconstituted and diluted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage and administration conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and

Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers ((b) (4) CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than (b) (4) hours at room temperature.

2. The preclinical studies were performed as a continuous infusion for 4 weeks in the rat and dog, and the identified NOAEL were 3 and 3.75 μg/kg/min which showed plasma concentration Css 113 and 61.5 ng/ml, respectively (males + females). The dosing regimen in the PCI setting is a bolus of cangrelor 30 μg/kg followed by 4 μg/kg/min infusion for 2 h, which achieved Css of 488 ng/ml. For a rapid acting and short-duration drug with no accumulation, the steady state plasma concentration appears to be a better comparator than the area under the concentration curve from administration to last measured concentration (AUC). Please provide a plot of concentration vs time profile of cangrelor plasma concentration in the rat and dog to estimate the margin of safety over the PCI setting PK profile.

3. The most notable toxicity findings in the preclinical studies were those related to the renal tubule and urinary tract, ranging from inflammation to necrosis, as shown by histological examinations. These tend to appear within 6 hours of administration of cangrelor at plasma concentrations of >250 ng/ml. Please comment the implications of these findings to the PCI setting which achieves plasma concentrations higher than the estimated threshold for potential toxicity in the kidney and ureter.

4. Please provide a plot of 'Percent platelet aggregation vs. Time' for platelet recovery following cessation of infusion of ARL 69931MX (40 or 60 μg/kg/min) for 7 days in the dog (Study No. SE 9861, Report No. PR 30152).

5. The protocol deviation criteria (such as infusion rate and infusion duration) are inconsistent between the PHOENIX Statistical Analysis Plan (SAP) and the clinical study report. Please clarify.

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

1. The **HIGHLIGHTS** of the PI are greater than one-half page. Please reduce the **HIGHLIGHTS** to only a half page.
2. In the **HIGHLIGHTS** Limitation Statement only the proposed tradename should be used. Please change, (b) (4) in this statement.
3. In the **INDICATIONS AN USAGE** section should not contain the established name or the route, therefore, please change:

(b) (4)

To

(b) (4) is a P2Y12 platelet inhibitor indicated.."

4. All cross-references throughout the label should be in italics (including the brackets) and all subsections should be within one set of parentheses and separated by a comma (e.g., (8.6, 8.7)). Please amend accordingly.
5. 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 (b) (4) practice." should be used verbatim and should precede the presentation of adverse reactions not follow them.
6. Please remove the trademark symbol (™) after each (b) (4) Placing the trademark symbol is only appropriate, in either the Highlights title or in the Section 1 after the first mention of the tradename.
7. 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"

8. Please delete section in the FPI that do not have any content (i.e., Section 15, **REFERENCES**).

We request that you resubmit labeling that addresses these issues by **August 2, 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, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and 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/

ALISON L BLAUS
07/12/2013

NORMAN L STOCKBRIDGE
07/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

REQUEST FOR METHODS VALIDATION MATERIALS

The Medicines Company
Attention: Stephen Sherman
Sr. Director of Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Stephen Sherman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [(b) (4)] (cangrelor) for injection, 50 mg/10mL vial.

We will be performing methods validation studies on [(b) (4)] (cangrelor) for injection, 50 mg/10mL vial, as described in NDA 204958.

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

Method, current version

Drug product ID, Assay and Content Uniformity by HPLC
Drug product Assay of Degradation Products by HPLC

Samples and Reference Standards

2 x 500 mg Cangrelor Reference Standard 3312.F
50 vials of [(b) (4)] (cangrelor) for injection, 50 mg/10mL vial
[(b) (4)] mg of impurity [(b) (4)]
mg of impurity [(b) (4)] if available
mg of impurity [(b) (4)] if available
mg of impurity [(b) (4)] if available
mg of impurity [(b) (4)] if available

Equipment

1 [(b) (4)]
1
1
1

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MICHAEL L TREHY
07/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

NDA ACKNOWLEDGMENT

The Medicine Company
Attention: Mr. Stephen Sherman
Sr. Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

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: (b) (4) (cangrelor) Injection, 50 mg

Date of Application: April 30, 2013

Date of Receipt: April 30, 2013

Our Reference Number: NDA 204958

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 June 29, 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. 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/

EDWARD J FROMM
05/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor) Alison Blaus, ODE 1/DCaRP, (301)796-1138
REQUEST DATE 16 May 2013	IND NO. 56812	NDA/BLA NO. 204958	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)

NAME OF DRUG: (b) (4) (cangrelor)	PRIORITY CONSIDERATION: Standard Review	CLASSIFICATION OF DRUG: NME	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting): **30 March 2014**
NAME OF FIRM: Medicines Company		PDUFA Date: 30 April 2014	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
X MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:

EDR Location: \\CDSESUB1\EVSPROD\NDA204958\0000

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: TBD (OPDP will be invited)

Labeling Meetings: Labeling Planning Meeting not yet scheduled but OPDP will be included.

Wrap-Up Meeting: n/a

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

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/s/

ALISON L BLAUS
05/16/2013

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: OSE	Alison Blaus, ODE 1/DCaRP, (301)796-1138

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
16 May 2013	56812	204958	NDA Submission	30 April 2013

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
cangrelor	Standard NDA Review	NME	30 January 2014

NAME OF FIRM: Medicines Company

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review these carton/container labels for this NDA, cangrelor.
EDR Location: \\CDSESUB1\EVSPROD\NDA204958\0000

PDUFA DATE: 30 April 2014

ATTACHMENTS: Draft Package Insert, Container and Carton Labels (please see these documents at the above EDR location.

CC: Archival IND/NDA 204958
HFD-110/Division File
HFD-110/RPM
HFD-110/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Alison Blaus	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

Reference ID: 3309706

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

/s/

ALISON L BLAUS
05/16/2013

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
THE MEDICINES CO Stephen Sherman 8 SYLVAN WAY PARSIPPANY NJ 07054 US	204-958

2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
973-290-6300	[X] YES [ ] NO
	IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:
	[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION
	[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME	6. USER FEE I.D. NUMBER
(b) (4) (Cangrelor)	PD3013265

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? [ ] YES [X] NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food,Drug, and Cosmetic Act
[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO
If a waiver has been granted, include a copy of the official FDA notification with your submission.

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes 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:

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor
Rockville, MD 20850

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor
Rockville, MD 20850

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.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
STEPHEN SHERMAN Stephen W Sherman	SR DIRECTOR, REGULATORY AFFAIRS	4/11/2013

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
(b) (4)

Form FDA 3397 (01/10)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 56812

MEETING MINUTES

The Medicines Company
ATTENTION: Stephen Sherman, Ph.D.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Sherman:

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

We also refer to the meeting between representatives of your firm and the FDA on 25 February 2013. The purpose of the meeting was to discuss the topline results from your CHAMPION-PHOENIX trial.

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

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Meeting Minutes
Sponsor's Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Topline Results
Meeting Category:	C
Meeting Date and Time:	25 February 2013 at 1430 – 1530 EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 56812
Product Name:	cangrelor
Proposed Indication:	Cangrelor is indicated for the reduction of cardiovascular thrombotic events, including stent thrombosis in patients with coronary artery disease who require $P2Y_{12}$ inhibition in an acute setting.
Sponsor Name:	The Medicines Company
Meeting Chair:	Norman Stockbridge, M.D., Ph.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
Martin Rose, M.D., JD	Clinical Reviewer
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Donald Jensen, Ph.D.	Pharmacology/Toxicology Reviewer
Edward Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D	Team Leader

* ***Office of Biostatistics***

James Hung, Ph.D.	Director, Biometrics I
Jialu Zhang, Ph.D.	Statistician

THE MEDICINES COMPANY ATTENDEES

Clive Meanwell, M.D.	Chairman and CEO
Jayne Prats, Ph.D.	Clinical Pharmacology
Jonathan Day, M.D., Ph.D.	Medical Director
Meredith Todd	Program Management
Simona Skerjanec, PharmD	Product Development
Stephen Sherman, JD, MBA	Global Regulatory Affairs
Tiepu Liu, M.D., Ph.D.	Senior Director, Biostatistics
Yanshan Ma, M.D.	Safety Monitor

(b) (4)

1.0 BACKGROUND

Cangrelor is a reversible, short-acting, parenteral inhibitor of platelet P2Y12 receptors. The Medicines Company (the sponsor) is developing cangrelor for (b) (4)

The Medicines Company (TMC) has completed the following clinical studies:

Phase 2

- ***BRIDGE*** – A randomized, double-blind, placebo-controlled study comparing administration of cangrelor to placebo in patients who had discontinued clopidogrel prior to coronary artery bypass grafting (CABG), attempting to maintain platelet inhibition until shortly before CABG. The primary efficacy endpoint was the proportion of subjects with P2Y12 Reaction Units (PRU) < 240 measured by the VerifyNow P2Y12 Test device during the entire period prior to CABG. The trial demonstrated that intravenous cangrelor at a dose of 0.75 µg/kg/min for several days consistently maintained platelet P2Y12 inhibition at PRU < 240.

Phase 3

- ***CHAMPION STUDIES*** - The primary endpoint in both studies was the composite of all-cause mortality, myocardial infarction, and ischemia-driven revascularization. Enrollment in both studies was terminated following an interim analysis indicating there was low likelihood of achieving the primary endpoint.
  - ***CHAMPION PCI*** - A randomized, double-blind, double-dummy, active-controlled, parallel group clinical trial in patients who required PCI, including patients with STEMI. Patients randomized to the cangrelor group received cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) for at least 2 hours or for the duration of the PCI procedure, whichever was longer, followed by 600 mg clopidogrel after the end of the infusion. Patients randomized to the clopidogrel group received a 600 mg loading dose of clopidogrel before the start of the PCI procedure.
  - ***CHAMPION PLATFORM*** - A randomized, double-blind, placebo-controlled, parallel group trial in patients with stable/unstable angina or NSTEMI who required PCI. Patients were randomized to receive either placebo or cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) prior to the procedure. Unlike Champion-PCI, patients in the control group did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure to both groups.
- ***PHOENIX*** - A randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective was to demonstrate that cangrelor reduces the risk of a composite of all cause mortality, myocardial infarction, ischemia driven revascularization, and stent thrombosis compared to clopidogrel.

TMC is planning a NDA submission in April 2013 which will include all of the above Phase 2 and 3 trials. This February meeting was scheduled to review the data from the PHOENIX trial.

2. DISCUSSION

2.1. Primary Efficacy and Safety Endpoint

- When TMC presented a Kaplan-Meyer plot of the primary efficacy endpoint, Dr. Zhang asked TMC to present a KM plot at the full resolution of the recorded time. She also stated that KM

plots of 1) of the primary endpoint for the time up to 6 hours after randomization and of 2) of stent thrombosis for the time up to 48 hours after randomization would be helpful. TMC stated ascertainment of stent thrombosis was made using the ARC definitions and that events occurring during PCI were included.

- When asked why the sponsor measured CKMB instead of troponin levels, the sponsor explained that in the CHAMPION studies it was difficult to discern the rise/fall of the troponin levels in patients with elevated troponin at baseline.

2.2. Study Design

- The Division asked if clopidogrel was administered after coronary angiography and before PCI or after completion of the procedure. TMC replied that it was at the discretion of the investigator. Approximately 75% of subjects were administered clopidogrel before PCI. TMC also noted that whether to administer 300 or 600 mg clopidogrel was at the discretion of the investigator. It appears that most sites used one dose or the other exclusively.
- Dr. Stockbridge asked whether clopidogrel could be administered before or during cangrelor infusion. TMC explained that based on PD data, they believe that clopidogrel active metabolite is blocked from interacting with the platelet P2Y12 receptor by cangrelor so clopidogrel should not be administered until after cessation of cangrelor infusion. The Division noted that if clopidogrel administration does not occur until cangrelor infusion is stopped, there will be a time during which there will not be effective platelet P2Y12 inhibition because it takes time to generate clopidogrel active metabolite.
- Dr. Marciniak observed that there is evidence that patients who are likely to undergo PCI should be pretreated with clopidogrel so that they have effective platelet P2Y12 inhibition at the time of PCI. He noted that patients pretreated with clopidogrel were excluded from CHAMPION and so the relative efficacy of cangrelor with a strategy of clopidogrel pretreatment is unknown.

2.3. Advisory Committee

- The Division stated that it was likely that the NDA would be discussed by an advisory committee.

2.4. Indication

- (b) (4)

2.5. (b) (4)

2.6. Format & Content

- Dr. Rose asked TMC to include in their submission an explanation of why cangrelor was successful in PHOENIX but not in the previous CHAMPION trials.
- Dr. Zhang agreed to review the sponsor's sample define file and/or "mock-up tables" to ensure that they are adequate to support the Agency's review of the submission.
- TMC stated that they will submit pharmacodynamic information about how to transition from cangrelor to ticagrelor while preserving the effectiveness of both drugs.

2.7. Post-meeting request

Please include in your NDA submission:

- Meeting minutes of all groups with any responsibility for the management of the trial, e.g. Executive Committee, Clinical Endpoint Committee, Steering Committee, and DMC. Please include agendas and copies of any presentations. For a meeting that was cancelled or where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
- All newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trial.

2.8. Post-Meeting Notes

The sponsor provided the following responses to the Division's post-meeting questions:

- Were subjects in PHOENIX genotyped for CYP2C19?

  Sponsor's Post-Meeting Response
  No.

- Were subjects taking omeprazole/esomeprazole at baseline excluded from enrolling in PHOENIX?

  Sponsor's Post-Meeting Response
  Yes, the use of CYP2C19 (e.g. omeprazole) was prohibited for the first 48 hours post-randomization.

- Was administration of proton-pump inhibitors (PPIs) recorded in the CRF? And if so, what level of information (e.g., type of PPI, start/stop, etc)?

  Sponsor's Post-Meeting Response
  No, excluded.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

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 investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order

to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues at the meeting that required further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The FDA Biometrics team agreed to review sample define files from BRIDGE to ensure that they are acceptable. The FDA requests adequate time to review these files (See section 2.6)	Sponsor	The date the sponsor agreed to provide these files was not established.

6.0 ATTACHMENTS AND HANDOUTS

The Medicines Company presented the attached slides at the 25 February meeting.

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

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

/s/

ALISON L BLAUS
04/03/2013

NORMAN L STOCKBRIDGE
04/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 56812

MEETING MINUTES

The Medicines Company
Attention: Meredith Todd, Senior Director
Program Management
8 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Todd:

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

We also refer to the teleconference between representatives of your firm and the FDA on 20 November 2012. The purpose of the meeting was to discuss the format and content of your planned dossier including the studies BRIDGE and CHAMPION.

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

If you have any questions, please call Alison Blaus, Regulatory Project Manager at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
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: 20 November 2012 – 1300 – 1400 EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903
Application Number: IND 56812
Product Name: Cangrelor for Injection
Proposed Indication: (b) (4)
Sponsor Name: The Medicines Company (MDCO)
Meeting Chair: Norman Stockbridge, M.D., Ph.D.
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
Mary Ross Southworth, PharmD	Safety Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Shari Targum, M.D.	Team Leader, Clinical Reviewer
Martin Rose, M.D., JD	Clinical Reviewer
Donald Jensen, Ph.D.	Pharmacology/Toxicology Reviewer
Alison Blaus	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D	Team Leader
TBD	Reviewer

* *Office of Surveillance and Epidemiology*

Allen D Brinker	Epidemiology
Reema Mehta	DRISK Team Leader
Kimberly Lehrfeld	DRISK Reviewer
Susan Lu	Epidemiology
Ling-Yu Wu	Epidemiology
Cherye Milburn	Regulatory Project Manager

* *Office of Biostatistics*

Jialu Zhang, Ph.D.	Statistician

* *Division of Scientific Investigation*

Sharon Gershon, Pharm.D.	Reviewer

* *Electronics Submissions Group*

Virginia Hussong	Reviewer
Douglas Warfield	Reviewer

THE MEDICINES COMPANY ATTENDEES

Brad Zerler	Pre-Clinical Drug Development
Jayne Prats, Ph.D.	Clinical Pharmacology
Jonathan Day, M.D., Ph.D.	Medical Director
Meredith Todd	Program Management
Peter Wijngaard, Ph.D.	Product Development
Rajeshwar Motheram, Ph.D.	Clinical Pharmacology
Simona Skerjanec, PharmD	Product Development
Stephen Sherman, JD, MBA	Global Regulatory Affairs
Tiepu Liu, M.D., Ph.D.	Senior Director, Biostatistics
Yanshan Ma, M.D.	Safety Monitor

1. BACKGROUND

Cangrelor for injection is a reversible inhibitor of the platelet P2Y12 receptor belonging to a different chemical class and with a different mechanism of action than ticagrelor. The Medicines Company (the sponsor) is developing cangrelor for (b) (4)

MDCO has completed two Phase 3 studies (CHAMPION PCI and CHAMPION PLATFORM) in which cangrelor administered as an IV bolus of 30 µg/kg followed by a 4 µg/kg/min infusion for up to 4 hours was compared to placebo on a background of clopidogrel for reducing all-cause mortality, myocardial infarction (MI), and ischemia driven revascularization (IDR) in primarily Acute Coronary Syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). Enrollment in both studies was terminated following an interim analysis indicating there was low likelihood of achieving the primary endpoint.

MDCO has also conducted a phase 2 trial (BRIDGE), which was a randomized, double-blind, placebo-controlled study comparing administration of cangrelor to placebo in patients who had discontinued clopidogrel prior to coronary artery bypass grafting (CABG), attempting to maintain platelet inhibition until shortly before CABG. The primary efficacy endpoint was the proportion of subjects with P2Y12 Reaction Units (PRU) < 240 measured by the VerifyNow P2Y12 Test device during the entire period prior to CABG. The device measures P2Y12 receptor occupancy, an indirect measure of degree of platelet inhibition by P2Y12 receptor blockers. The trial demonstrated that intravenous cangrelor at a dose of 0.75 µg/kg/min for several days consistently maintained platelet P2Y12 inhibition at PRU < 240 and the proportion of cangrelor patients who were in this range was significantly smaller than the proportion of placebo subjects.

MDCO is currently conducting another Phase 3 trial (PHOENIX), which is a randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective is to demonstrate that cangrelor reduces the risk of a composite of all cause mortality, myocardial infarction, ischemia driven revascularization, and stent thrombosis compared to clopidogrel. PHOENIX is an event driven trial and database lock may occur as early as January 2013.

This meeting was scheduled to discuss the format and content of the potential NDA submission based on the results of BRIDGE, with support from the CHAMPION studies, (b) (4)

2. DISCUSSION

2.1. Questions for the FDA

Clinical & Statistical

1. MDCO proposes including the necessary data in the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) to replace the need for both the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS). Additional tables and figures can be placed in Module 5, if necessary. Does the Agency agree that the ISS and ISE are not necessary if adequately addressed in the SCS and SCE?

   FDA Preliminary Response
   The NDA should include an ISE, ISS, and the Summaries of Clinical Safety and Efficacy.

   Medicines Company Preliminary Response
   Based upon our response below to Question #2, MDCO believes that we can present the analyses necessary to adequately provide the Division with what is required in the ISS and ISE within the Summary of Clinical Safety and Summary of Clinical Efficacy. If the appendices, etc. go beyond the page limit of the SCS and SCE, then MDCO can place those in Module 5. Does the Agency agree?

   Discussion at the Meeting
   Dr. Rose explained that there are important analyses that are included in the ISE/ISS that are not included in the Clinical Overview. Dr. Stockbridge suggested that MDCO submit a "dummy" ISE/ISS and include a cross-reference (& hyperlink) to the analogous section of the Clinical Overview where that information could be found. For those analyses that do not have a corresponding section in the Clinical Overview, the Division asked MDCO to complete that section of the ISE/ISS.

   When asked about the timing of the CHAMPION PHOENIX data, the sponsor explained that depending on timing, they may have unblinded data by the 120-day safety update. Dr. Rose asked MDCO to include the primary efficacy and safety data in the update, and if available, the clinical study report. MDCO agreed.

2. [redacted] (b) (4) Does the Agency agree?

   FDA Preliminary Response
   For the indication you propose, patients may be treated with cangrelor for several days. Few of the clinical studies of cangrelor have studied patients dosed for more than 4 hours. [redacted] (b) (4)
   We suggest the following groupings for studies for your safety analyses:
   - All studies
   - All studies excluding volunteer studies
   - All controlled studies

- All placebo-controlled studies
- All active-controlled studies
- CHAMPION PCI and PLATFORM pooled
- CHAMPION PCI and PLATFORM separately
- BRIDGE

Medicines Company Preliminary Response
MDCO will conduct the analyses suggested by the Division. Descriptions of the individual studies that will be included in the analyses are provided below followed by a table of the studies that comprise the groups suggested by the Division (please refer to the formal submission for this table).

Discussion at the Meeting
The Division acknowledged MDCO's response and agreed that this was acceptable.

3. MDCO proposes to [redacted] (b) (4) Does the Agency agree?

FDA Preliminary Response
No. In evaluating efficacy we believe most of the relevant data will come from BRIDGE, including both the pharmacodynamic data and clinical event data. The CHAMPION studies should be presented as individual trials and analyzed as specified in their protocols. We do not believe [redacted] (b) (4)

Discussion at the Meeting
The Division reiterated that they are not [redacted] (b) (4)

4. The following plan provides details concerning the submission of datasets (Table 2). Data preparation for [redacted] (b) (4)

Does the Agency agree?

FDA Preliminary Response
In general, you should submit complete datasets for all studies of cangrelor. Datasets should be uniformly structured to allow for analyses, and complete information (such as definitions files) should be provided. The datasets should be (b) (4) as suggested (see Question 2 response). You should provide sufficient details and SAS code (where applicable) of your raw data cleaning methods in order to understand how you created the analyses datasets. Your application may be considered incomplete without such information.

Medicines Company Preliminary Response
MDCO is planning on converting the raw datasets for all the studies of cangrelor clinical trials into SDTM format. Does this address the Agency's request for uniformly structured datasets?
Additionally, some of the Phase 1 and 2 legacy studies were conducted by a different company and MDCO may not have all of the analyses datasets for these studies. MDCO will provide analysis datasets and SAS codes for (b) (4) safety data per Question 2 with sufficient details of derivation in the Define file. MDCO will provide analyses datasets and programs with limited documentation (defined file without all derivation algorithms included) for the individual legacy trials. Is that acceptable to the Agency?

Discussion at the Meeting
MDCO clarified that they will submit raw and SDTM datasets, but do not have some of the analysis datasets from a few of the legacy trials conducted by AstraZeneca. The Division suggested that MDCO state in the NDA for which studies they do not have the analysis datasets. The Division further explained that the Medicine's Company is responsible for assuring that all analyses submitted in the NDA are accurate. The Division suggested MDCO consider reanalyzing and verify the data from these studies.

5. MDCO is planning on submitting data from observational registries (The Dutch Registry) to quantify the absolute incidence of ST in patients who discontinue oral P2Y12 inhibitors. MDCO is planning to provide the raw data used in the analysis in SAS transport file format. Does the Agency agree?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion on this topic.

Chemistry, Manufacturing, and Controls (CMC)

1. MDCO intends to propose a shelf life of (b) (4) months for the drug product, Cangrelor for Injection, based on available real time stability data for up to (b) (4) months and accelerated stability data for up to six months from six registration stability batches manufactured at two different sites (not the proposed commercial site).
MDCO will also file with three months real time and accelerated stability data from the ongoing stability program from two representative commercial scale batches manufactured at the proposed commercial manufacturing site with a commitment to place the first three

commercial batches on long term and accelerated stability. The manufacturing process and container closure system for the drug product is the same at all manufacturing sites presented. The rationale and stability data from the six registration stability batches are provided in Appendix 4. Does the Agency agree with this approach?

FDA Preliminary Response
Your approach is reasonable. The assignment of the shelf life for the product will be determined during the NDA review.

Discussion at the Meeting
No further discussion on this topic.

Pre-Clinical

1. Pre-clinical safety program was conducted in the mid 1990's. During this time, ICH safety pharmacology guidelines were not in place. As a result, most of the safety pharmacology studies including CNS evaluation in mice and cardiovascular evaluation in dogs did not contain written assurance of GLP compliance with the exception of a single-dose cardiovascular and respiratory study in rats. Despite the non-GLP status noted for the safety pharmacology studies, MDCO believes that the results support the development and registration of cangrelor because no adverse results in the secondary and safety pharmacology studies were observed that would preclude the use of cangrelor. Does the Agency agree?

   FDA Preliminary Response
   Yes, we agree.

   Discussion at the Meeting
   No further discussion on this topic.

2. Neither cangrelor nor its primary plasma metabolite (AR-C69712XX) were screened in the hERG assay, but an in vitro assay and multiple studies in dogs (including repeat dose toxicology) that were conducted have not indicated a potential for prolongation of the QT interval of the ECG. Moreover, in a definitive clinical trial (TMC-CAN-08-01) designed to determine the effect of cangrelor on the QTc interval, the results indicate that cangrelor has no effect on cardiac repolarization. Thus, MDCO believes that the effect of cangrelor on cardiac repolarization has been resolved. Does the Agency agree?

   FDA Preliminary Response
   Yes, we agree.

   Discussion at the Meeting
   No further discussion on this topic.

Regulatory

1. MDCO is requesting a pediatric waiver for the proposed indication above because the need for bridging from oral P2Y12 platelet inhibitors to cardiac surgery is either rare or nonexistent in the pediatric population. Does the Agency agree?

FDA Preliminary Response
The Division agrees that a waiver appears appropriate. However, your request for a waiver will be reviewed by the Pediatric Review Committee (PeRC) after your NDA is submitted and they will decide whether to grant a waiver.

Discussion at the Meeting
No further discussion on this topic.

2. MDCO is not planning on developing a risk management plan. Does the Agency agree?

FDA Preliminary Response
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion at the Meeting
No further discussion at the meeting.

3. At the 120-Day update, MDCO is planning to submit the SUSARs from the ongoing CHAMPION PHOENIX trial. Does the Agency agree?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion at the meeting.

Electronic Submission

1. The Medicines Company intends to submit in the Electronic Technical Document Format (eCTD) according to the Guidance entitled "Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications". Does the Agency agree?

FDA Preliminary Response
Yes. Please also refer to the eCTD website for eCTD Guidance and Specifications located at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Discussion at the Meeting
No further discussion at the meeting.

Labeling

1. The proposed labeling with this application will be provided in both Structured Product Labeling (SPL) and in Microsoft WORD format. Does the Agency agree?

FDA Preliminary Response
Yes. For archival purposes, please also submit a PDF version of the labeling document submitted in Word. Also, when you submit word documents, please make sure the leaf title includes "Word", so reviewers would quickly identify it.

Discussion at the Meeting
No further discussion at the meeting.

2. All additional labeling components (eg, carton, containers, etc) will be provided as PDF files. Does the Agency agree?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion at the meeting.

Case Report Tabulations

1. With the submission of the datasets, individual patient listings (Appendix 16.4) will not be included with the clinical study reports. Similarly, patient case report forms (Appendix 16.3) will be provided separately and not appended to the clinical study reports. However, Appendix 16.2, Patient Data Listing, will be included with the report. Does the Agency agree?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion at the meeting.

2. A study tagging file (STF) will be provided for each study report, which will identify all the components of the study report, including all associated case report forms and datasets. The STF will allow navigation to these components. Does the Agency agree?

FDA Preliminary Response
Yes. Please make sure all granular documents are properly tagged.

Discussion at the Meeting
No further discussion at the meeting.

3. SAS datasets will be provided in lieu of case report tabulations in accordance with the 1999 FDA guidance's, "Providing Regulatory Submissions in Electronic Format – General Considerations," and "Providing Regulatory Submissions in Electronic Format – NDAs." Separate patient profiles, in PDF format, are not planned to be submitted. Does the Agency agree?

Each dataset will be provided as a SAS transport file in accordance with the above referenced guidance. Both raw and analysis datasets (where available) will be provided. Does the

Agency agree?

FDA Preliminary Response
Yes.

Discussion at the Meeting
No further discussion at the meeting.

Case Report Forms (CRFs)

1. MDCO is planning on including the following CRFs and narratives in the NDA, Deaths, SAEs, and discontinuations due to AEs. Does the Agency agree?

   FDA Preliminary Response
   You proposal regarding narratives is acceptable, but please provide all CRFs from BRIDGE, CHAMPION PCI, and CHAMPION PLATFORM. Also include CRFs for subjects in any trial who had a CABG within one week of drug exposure.

   Discussion at the Meeting
   No further discussion on this topic.

2. All CRFs will be provided as PDF files, organized by study, site and patient. They will be bookmarked by visit and domain, as well as provide a hypertext link from all data clarification forms to the corrected page. An audit trail will be provided to identify the queries during the conduct of the trial. However, due to the nature of Electronic Data Capture (EDC), hyperlinks are not necessary between the audit trail and the pertinent fields. Does the Agency agree?

   FDA Preliminary Response
   No. Hyperlinks between the audit trail and the pertinent fields are useful.

   Medicines Company Preliminary Response
   MDCO will hyperlink to the CRF page. Does the Agency agree?

   Discussion at the Meeting
   The Division agreed that this was acceptable.

2.2. Additional FDA Requests

1. Please submit all SAS codes used and all data sets used to produce the main tables and figures in your ISE, SCE, ISS, SCS. For example, if a SAS code contains a macro, please include the macro code.

   Discussion at the Meeting
   No further discussion on this topic.

2. Please submit MedDRA coding dictionaries for bleeding related AEs and any other significant AEs for cangrelor as SAS transport files.

Medicines Company Preliminary Response
All AEs will be recoded to MedDRA v 13.1. In the MDCO studies TMC-CAN-05-02, TMC-CAN-05-03, and TMC-CAN-08-02 bleeding is captured in a structured approach in bleed datasets separate from AE datasets. The bleeding datasets from these three trials will be submitted in SAS transport files in SDTM format. Additionally, these will be mapped to MedDRA v 13.1 preferred terms and provided in AE analyses datasets as SAS transport files. Does the Agency agree?

Discussion at the Meeting
The sponsor added to their preliminary response noting that the dictionaries will be provided and bleeding will also be mapped to MedDRA as requested.

3. Please submit a table detailing all of the main tables and figures featured in the clinical efficacy and safety sections of the NDA. The table should contain the following:
   - title of the table or figure in NDA
   - a hyperlink to the location of the table or figure with page number
   - a hyperlink to the SAS code used to create the table or figure
   - name of the dataset(s) used to create the table or figure.

   Medicines Company Preliminary Response
   It is MDCO interpretation that this request pertains to only the SCS and SCE, is that correct?

   Discussion at the Meeting
   Dr. Stockbridge clarified that this table would be helpful for all of the primary studies for which their NDA relies, BRIDGE, CHAMPION-PCI, & CHAMPION-PLATFORM.

4. Please provide sample clinical trial kits, identical to those used during BRIDGE. One kit from the placebo arm and another from cangrelor should be provided to Ms. Blaus' desk address.

   Medicines Company Preliminary Response
   It is MDCO's understanding that the Division would like to obtain sample kits of the active and placebo used in the BRIDGE trial. MDCO will supply one sample kit that does not contain clinical trial study medication. Moreover, the kit was the same for both active and placebo. Is this acceptable?

   Discussion at the Meeting
   The Division explained that they were requesting the clinical trial kits from both arms (active & placebo) of BRIDGE. MDCO later confirmed that they would be able to provide kits from both arms.

5. Please include all charters for committees involved in conducting BRIDGE, CHAMPION PCI, and CHAMPION PLATFORM (e.g., DSMB, Steering Committee, etc.).

   Discussion at the Meeting
   No further discussion on this topic.

6. Please include Steering Committee and DSMB meeting minutes (including any data/slides presented to the Committee) for BRIDGE, CHAMPION PCI, and CHAMPION PLATFORM. For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the cangrelor clinical

team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

Medicines Company Preliminary Response
MDCO will add these as appendices to the respective CSRs, but requests guidance on naming and format (individual packages or one file).

Discussion at the Meeting
MDCO's preliminary response was acknowledged and the Division agreed that the appendix of the CSR was the appropriate location for these documents. The Division added that the minutes should be divided by type of committee and then bookmarked by date. It also requested that if there were not meeting minutes available for a certain date that a place holder for that meeting be included with a signed document from the Medicine's company acknowledging that no minutes were taken for that meeting. MDCO agreed.

7. A description of the responsibilities of each ARO or CRO used in BRIDGE, CHAMPION PCI, and CHAMPION PLATFORM.

Medicines Company Preliminary Response
These responsibilities are included in the CSRs for each study.

Discussion at the Meeting
No further discussion on this topic.

8. Please provide all versions of your clinical trial monitoring plan for BRIDGE, CHAMPION PCI, and CHAMPION PLATFORM.

Discussion at the Meeting
No further discussion on this topic.

9. Please provide all versions of your detailed data management plan, including both manual and programmed data checks used throughout the study BRIDGE, CHAMPION PCI, and CHAMPION PLATFORM.

Discussion at the Meeting
No further discussion on this topic.

10. Attached as an appendix to these preliminary responses is an information request provided by the Office of Scientific Investigations (Appendix I). This document includes data requests that are to be addressed in your initial submission. This applies only to BRIDGE.

Medicines Company Preliminary Response
MDCO will provide the general study related information and specific Clinical Investigator information for the BRIDGE clinical trial as requested. Within the first 30 days after filing, is it acceptable for MDCO to provide the Subject Level Data Listings by Site and Site Level Dataset after the NDA is submitted?

Discussion at the Meeting
Dr. Stockbridge and OSI explained that these data were not required but rather strongly encouraged. The answer to this question was further complicated by whether the sponsor was (b) (4) The Agency agreed that it would be acceptable to

provide by 30 days after their initial submission, (b) (4) .

11. Also attached to these minutes is the Clinical Pharmacology Review Aid (Appendix II). Please refer to this document when putting together clinical pharmacology information in your dossier.

Discussion at the Meeting
No further discussion at the meeting.

12. We understand that neither thrombotic nor bleeding events were adjudicated in BRIDGE. If we are mistaken, please provide the adjudication committee charter, all adjudication packages, and an adjudication data file. We will provide further details about the adjudication data file if there was adjudication.

Discussion at the Meeting
No further discussion at the meeting.

13. Please provide the following information from BRIDGE:
    - Information on the relationship between drug-related parameters (such as the amount of time between the termination of the study drug infusion and the first CABG incision, or the value of the pre-incisional PRU), and the amount of CABG-associated bleeding or transfusions
    - Information on the relationship between drug-related parameters before or during the study drug infusion (such as the number of hours between the last dose of clopidogrel and the start of the study drug infusion, or on-drug PRU values), and the risk of bleeding during the study drug infusion.

Discussion at the Meeting
No further discussion at the meeting.

14. Please discuss the value of using Verify-Now results for determining the type and dose of thienopyridine and other platelet P2Y12 inhibitors. In this discussion, you may wish to include information from the following studies:
    - GRAVITAS
    - TRIGGER-PCI
    - ARCTIC
    - TRILOGY-ACS

Discussion at the Meeting
The sponsor acknowledged the Divisions requests and agreed to provide it in the dossier.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. All information discussed at the meeting is expected in the initial submission, with one caveat. Dr. Stockbridge and OSI explained that the need for the site selection tool datasets would hinge on the review status requested, priority or standard review (see section 2.2, question 10). The Agency

agreed that it would be acceptable to provide within 30 days after their initial submission, (b) (4) .

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

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

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 investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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 no issues raised that required further discussion.

5.0 ACTION ITEMS

There were no action items for either the Agency or the sponsor.

6.0 ATTACHMENTS AND HANDOUTS

There were no slides or handouts for this meeting.

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

/s/

NORMAN L STOCKBRIDGE
12/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 56812

MEETING MINUTES

The Medicines Company
Attention: Meredith Todd, Senior Director
Program Management
8 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Todd:

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

We also refer to the teleconference between representatives of your firm and the FDA on 15 August 2012. The purpose of the meeting was to discuss a number of follow-up items to our 14 May 2012 End-of-Phase 3 meeting which discussed the data from your BRIDGE study and a possible dossier submission combining these data with the results of your completed CHAMPION studies.

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

If you have any questions, please call Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance
Meeting Date and Time: 15 August 2012 from 1300-1400 EST
Meeting Location: Teleconference
Application Number: IND 56812
Product Name: cangrelor for injection
Indication: [redacted] (b) (4)

Sponsor Name: Medicines Company
Meeting Chair: Ellis F. Unger, M.D.
Meeting Recorder: Alison Blaus

FDA ATTENDEES

* *Office of New Drugs, Office of Drug Evaluation I*	
Ellis F. 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
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Martin Rose, M.D., JD	Clinical Reviewer
Karen Hicks, M.D.	Clinical Reviewer
Alison Blaus	Regulatory Health Project Manager
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D	Team Leader
* *Office of Biostatistics*	
John Lawrence, Ph.D.	Mathematician

SPONSOR ATTENDEES

Clive Meanwell M.D., Ph.D.	Chairman and CEO
Simona Skerjanec PharmD	Vice President, Chest Pain Care Pathway
Peter Wijngaard Ph.D.	Vice President, Innovation Leader
Markus Dietrich M.D.	Medical Director
Jayne Prats Ph.D.	Vice President, Global Knowledge
Tiepu Liu M.D., Ph.D.	Senior Director, Biostatistics
Meredith Todd	Senior Director, Program Management
[redacted] (b) (4)	

1.0 BACKGROUND

Cangrelor for injection is a non-thienopyridine reversible inhibitor of the P2Y12 platelet receptor. The Medicines Company (the sponsor) is developing cangrelor for (b) (4)

The sponsor has previously completed two Phase 3 studies in which cangrelor administered as an IV bolus of 30 µg/kg followed by a 4 µg/kg/min infusion for up to 4 hours was compared to placebo on a background of clopidogrel for reducing all-cause mortality, myocardial infarction (MI), and ischemia driven revascularization (IDR) in primarily Acute Coronary Syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). Enrollment in both studies was terminated following an interim analysis indicating there was low likelihood of achieving the primary endpoint.

The sponsor has also conducted a phase 2 trial (BRIDGE), which was a randomized, double-blind, placebo-controlled study comparing administration of cangrelor to placebo in patients who had discontinued clopidogrel prior to coronary artery bypass grafting (CABG), attempting to maintain platelet inhibition until shortly before CABG. The primary efficacy endpoint was the proportion of subjects with P2Y12 Reaction Units (PRU) < 240 measured by the VerifyNow P2Y12 Test device during the entire period prior to CABG. The device measures P2Y12 receptor occupancy, an indirect measure of degree of platelet inhibition by P2Y12 receptor blockers. The trial demonstrated that intravenous cangrelor at a dose of 0.75 µg/kg/min for several days consistently maintained platelet P2Y12 inhibition at PRU < 240 and the proportion of cangrelor patients who were in this range was significantly smaller than the proportion of placebo subjects.

The sponsor is currently conducting another Phase 3 trial (PHOENIX), which is a randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective is to demonstrate that cangrelor reduces the risk of a composite of all cause mortality, MI, IDR and stent thrombosis compared to clopidogrel. PHOENIX is an event driven trial and database lock may occur as early as January 2013.

This meeting is a follow-up to our 14 May 2012 discussion at which a potential NDA submission was discussed that would be based on the results of BRIDGE, with support from CHAMPION, for the bridging indication.

2. DISCUSSION AT THE MEETING

2.1. BRIDGE Data

Dr. Unger began the discussion highlighting some of the concerns that the Agency still has with a potential dossier based solely on a Pharmacodynamic (PD) marker. It is clear that this NDA would be seeking an approval based on the ability of cangrelor to inhibit platelet function and an assumption that the effect on the surrogate endpoint would help in preventing stent thrombosis. The Agency noted that the basis for reliance on this surrogate in this specific case would need to be strengthened in the dossier, beyond that which was provided in the backgrounder.

The Agency also expressed an interest in knowing the absolute risk of stent thrombosis during the period of withdrawal of clopidogrel. The sponsor explained that they are limited to only the data from the Dutch Stent Thrombosis Registry in the 2009 van Werkum publication (JACC 53: 1399-409). At this time, the sponsor has the days of clopidogrel treatment, outcome data, demography and the days from PCI to stent thrombosis. The Division asked the sponsor to calculate the actual event rate in those patients who discontinued clopidogrel and include it in the dossier and to also include, if possible, information on whether the stent was a drug eluding stent (DES) or bare metal stent (BMS) as well as the diameter and length of the stent. The sponsor said that they might be able to get data on DES vs. BMS and length but they will check on whether they can obtain diameter.

2.2. CHAMPION Studies

The Agency noted that the sponsor must address the implications of the CHAMPION study and provide a rationale to explain why the outcome of that failed trial has no impact on use of the BRIDGE data or the indication sought. The sponsor acknowledged the Agency's concern, and said that they would include such information in the dossier.

2.3. Platelet Aggregation Assay

It was stressed to the Medicines Company that they need to document how the platelet aggregation assays were done and that their results correlate well with outcome. The sponsor explained that they used the VerifyNow assay in both CHAMPION and BRIDGE and will include information on how the assays were performed. It was noted that the VerifyNow assay has not been cleared by the Center for Devices and Radiological Health for use in guiding therapy.

2.4. General Dossier Discussion and Requests

- The Division asked the sponsor to also include clear dose and duration instructions for the indication sought and a solid rationale for both. The information on duration should include information on when to initiate cangrelor and when to discontinue it.
- When discussing timing of the potential NDA submission, the sponsor stated that they will plan to submit this year and will not wait for the PHOENIX results to be known. The results of PHOENIX will be known in 1Q2013.

3.0 OTHER IMPORTANT INFORMATION

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

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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.

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1.				
2.				

Corresponding names and titles of onsite contact:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no outstanding issues raised at the meeting that required further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no slides or handouts for this meeting.

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

/s/

ELLIS F UNGER
09/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 56812

MEETING MINUTES

The Medicines Company
Attention: Meredith Todd, Senior Director
Program Management
8 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Todd:

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

We also refer to the meeting between representatives of your firm and the FDA on May 14, 2012. The purpose of the meeting was to discuss the data from your BRIDGE study and a possible dossier submission combining these data with the results of your completed CHAMPION studies.

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
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Phase 3 Data Top-line
Meeting Date and Time:	May 14, 2012 15:30 – 17:00 EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 56812
Product Name:	cangrelor for injection
Proposed Indication:	(b) (4) [redacted]
Sponsor/Applicant Name:	The Medicines Company
Meeting Chair:	Ellis Unger, M.D.
Meeting Recorder:	Alison Blaus

FDA ATTENDEES

Center for Drug Evaluation & Research

* *Office of New Drugs, 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
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Martin Rose, M.D.	Clinical Reviewer
Preston Dunnmon, M.D.	Clinical Reviewer
Alison Blaus	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*

Rajanikanth Madabushi, Ph.D	Team Leader

* *Office of Biostatistics*

Hsien Ming J Hung, Ph.D.	Director, Division of Biometrics I
John Lawrence, Ph.D.	Statistician

Center for Devices and Radiological Health & Research

* *Office of In Vitro Diagnostic Device Evaluation and Safety*

Robert Becker	Team Leader, Clinical Reviewer

* *Office of In Vitro Diagnostic Device Evaluation and Safety, Division of Immunology and Hematology Devices*

Maria M Chan	Supervisory Microbiologist
Abraham Tzou	Clinical Reviewer

SPONSOR ATTENDEES

Clive Meanwell M.D.,Ph.D.	Chairman and CEO
Simona Skerjanec PharmD	VP, CV Portfolio Lead
Peter Wijngaard Ph.D.	Vice President, Cangrelor Development Lead
Markus Dietrich M.D.,Ph.D.	Medical Director
Jayne Prats Ph.D.	VP, Thrombosis and Vascular Biology Programs
Tiepu Liu M.D.,Ph.D.	Senior Director, Biostatistics
Meredith Todd	Senior Director, Program Management
[redacted] (b) (4)	

1.0 BACKGROUND

Cangrelor for injection is a non-thienopyridine reversible inhibitor of the P2Y12 platelet receptor. The Medicines Company (the sponsor) is developing cangrelor for [redacted] (b) (4)

The sponsor has previously completed two Phase 3 studies in which cangrelor administered as an IV bolus of 30 µg/kg followed by a 4 µg/kg/min infusion for up to 4 hours was compared to placebo on a background of clopidogrel for reducing all-cause mortality, myocardial infarction (MI), and ischemia driven revascularization (IDR) in primarily ACS patients undergoing percutaneous coronary intervention (PCI). Enrollment in both studies was terminated following an interim analysis indicating there was low likelihood of achieving the primary endpoint.

The sponsor has also conducted a phase 2 trial (BRIDGE), which was a randomized, double-blind, placebo-controlled study comparing administration of cangrelor to placebo in patients who had discontinued clopidogrel prior to coronary artery bypass grafting (CABG), attempting to maintain platelet inhibition until shortly before CABG. The primary efficacy endpoint was the proportion of subjects with P2Y12 Reaction Units (PRU) < 240 measured by the VerifyNow P2Y12 Test device during the entire period prior to CABG. The device measures P2Y12 receptor occupancy, an indirect measure of degree of platelet inhibition by P2Y12 receptor blockers. The trial demonstrated that intravenous cangrelor at a dose of 0.75 µg/kg/min for several days consistently maintained platelet P2Y12 inhibition at PRU < 240 and the proportion of cangrelor patients who were in this range was significantly smaller than the proportion of placebo subjects.

The sponsor is currently conducting another Phase 3 trial (PHOENIX), which is a randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective is to demonstrate that cangrelor reduces the risk of a composite of all cause mortality, MI, IDR and stent thrombosis compared to clopidogrel. PHOENIX is an event driven trial and database lock may occur as early as January 2013.

At this meeting, the sponsor would like to gain Agency input on a potential NDA submission that would be based on the results of BRIDGE, with support from CHAMPION, for the bridging indication described on the first page of these minutes.

2.0 QUESTIONS FOR THE FDA AND DISCUSSION

1. Currently a treatment dilemma exists as there are no approved or adequate treatments to bridge the period between discontinuation of oral platelet P2Y12 inhibitors and surgery.

   Clinical evidence has informed practice guidelines and current FDA-approved labeling in the Warnings and Precautions section of oral P2Y12 inhibitors. The wording of such labeling is as follows:

   - Patients who continue oral P2Y12 inhibitors and who undergo coronary artery bypass grafting surgery (CABG), or other surgical procedures are at increased risk of bleeding. Discontinuation of oral P2Y12 inhibitors is recommended at least 5-7 days prior to any surgery.
   - Patients who prematurely discontinue oral P2Y12 inhibitors for surgery will be at increased risk for cardiac events, such as stent thrombosis, myocardial infarction, and death. Lapses in therapy should be avoided.

   Currently, care-givers have to manage patients to one of two risks: Continue oral agents and risk bleeding or discontinue oral agents and risk thrombosis. Does the Agency agree that there is a medical need for an agent that can bridge between oral platelet P2Y12 inhibitor discontinuation (and attendant risks of coronary thrombosis) and surgery that carries a high risk of bleeding?

   FDA Preliminary Response
   In principle, yes. However the magnitude of potential benefit is dependent on 1) the absolute risk of significant thrombotic events such as death, MI, and stent thrombosis in the recommended 5-7 day period between clopidogrel discontinuation and surgery in various groups of patients and 2) the absolute increase in the risk of significant bleeding before or during various types of surgery after discontinuing clopidogrel vs. waiting until there is no residual effect of clopidogrel. In your meeting with us please be prepared to discuss any data you have about the magnitude of these risks.

   Discussion at the Meeting
   The sponsor stated they believe that the principal benefit of administering cangrelor is prevention of stent thrombosis. Drs Rose and Temple stated that any study describing the risk of discontinuing clopidogrel would be helpful in a potential dossier. The Division added, however, that the sponsor should ensure that the results are not confounded by surgery, as they might have been in one study in patients with hip fractures cited by the sponsor. In addition, the risk of discontinuing clopidogrel alone should be distinguished from the risk of discontinuing both clopidogrel and aspirin.

   The Division also observed that two distinct patient populations were studied in BRIDGE:

   - Patients who underwent catheterization for ACS and then underwent urgent CABG. Probably most of these patients were administered one or a few doses of thienopyridine as treatment for ACS and probably most had not undergone coronary stent placement.
   - Patients who had been on clopidogrel chronically for prevention of stent thrombosis and underwent elective CABG.

The risks and benefits of discontinuing clopidogrel prior to surgery may be dissimilar in the two populations. The Division asked the sponsor to submit information about the risks and benefits of discontinuance of clopidogrel for a follow-up meeting.

2. The BRIDGE trial demonstrated in patients with CAD who required premature discontinuation of oral P2Y12 inhibition prior to cardiac surgery, that intravenous cangrelor achieved and maintained a level of P2Y12 inhibition known to be associated with a reduced risk of thrombotic events up until the time of cardiac surgery, without a significant excess in surgical bleeding complications.

   Does the Agency have any comments regarding the results and conclusions from the BRIDGE study? Is the pharmacodynamic measure of platelet activity, together with data showing lack of clinical ischemic events in BRIDGE, sufficient to demonstrate effectiveness in this setting when supported by clinical events data from other large, adequate and well-controlled trials in the a closely related population? (b) (4)

FDA Preliminary Response

You assert that you have identified a level of P2Y12 inhibition as measured by the VerifyNow P2Y12 test known to be associated with a reduced risk of thrombotic events. We are interested in the data you have to support that assertion. In particular, we are interested in any data you may have describing the relationship between P2Y12 inhibition and outcomes, both thrombotic and hemorrhagic. Does the level of desirable platelet inhibition vary depending on proximity to the event (ACS or stent implantation) that resulted in administering clopidogrel?

We believe that any level of inhibition of platelet aggregation is likely to be associated with some reduction in risk for thrombotic events on the basis of the outcomes of multiple clinical trials. It is likely there is some level of inhibition of platelet aggregation so low that that risk reduction is not detectable and some level above which there is no further risk reduction. We also believe the inverse relationship holds for bleeding risk. The challenge for anti-platelet drug development is to find a dose that appropriately balances risk and benefit. It is not clear how you have determined that the target level of P2Y12 inhibition chosen as the primary endpoint in BRIDGE appropriately balances risk and benefit. We note that in the GRAVITAS trial, post-PCI patients with levels of PRU (termed "high on-treatment platelet reactivity") above the level targeted in BRIDGE were randomized to standard and high doses of clopidogrel. Despite a significant reduction of proportion of patients with "high on-treatment" reactivity in the high dose clopidogrel group, the proportion of patients with death, MI, stent thrombosis were identical in both groups. And the proportion of patients with GUSTO severe or major bleeding was actually higher in the patients randomized to standard doses of clopidogrel, i.e. with higher mean PRU. These data suggest that treatment-driven changes in VerifyNow-based PRU results may not be useful in predicting the risk of either CV events or bleeding complications.

It seems to us that outcomes in this indication may depend not so much on time above and below some level of platelet inhibition but rather on the increase in platelet inhibition resulting from administration of cangrelor. Please provide a comparison of the observed

PRUs for each group by day of treatment. You might want to describe these outcomes by use of medians with interquartile range and outliers.

If the level of platelet inhibition you have chosen satisfactorily balances risk and benefit, then a fixed dose of your product might not be an appropriate dosing strategy. The inter-individual variability in response to clopidogrel as measured by platelet aggregation is known to be high, and loss of clopidgrel's effect after discontinuation may be variable. The use of a titrated dose based on the level of platelet inhibition might improve the benefit/risk profile of treatment with cangrelor and better define the necessary duration of treatment.

Discussion at the Meeting

Dr. Meanwell acknowledged that the clinical utility of the specific cut-point of PRU <240 is not known. While a clinical outcome trial would be ideal, one cannot be realistically performed. The rate of thrombotic events in this clinical situation (very brief period) means that an outcome trial would need to be very large and the potential market for this indication is not large enough to justify such a large outcome trial financially. Dr. Unger asked, if thrombotic events are infrequent, the possible absolute decrease in thrombotic events is very small, and the number of patients that would need to be treated to prevent an event is very large, how valuable is any therapy in that situation. The sponsor acknowledged Dr. Unger's question and will address it in their follow-up meeting document.

The sponsor stated that they believe that the clinical utility of the specific PRU value used in the trial is not critical and are not suggesting it is a surrogate for efficacy. Rather the difference between the PRU levels in the two treatment groups is so large that there must be a substantial reduction in the risk for thrombotic events.

3. The Medicines Company would like to discuss with the Agency a New Drug Application (NDA) filing strategy to expedite the availability of cangrelor. The NDA submission would include the BRIDGE trial, and supportive pharmacodynamic, clinical efficacy and safety data from the two adequate and well-controlled CHAMPION trials conducted in over 14,000 patients undergoing PCI.

   We suggest that the NDA could pursue the following (or similar) indication:

   Does the Agency agree with this NDA filing strategy?
   Does the Agency have a view of the likelihood that this package would provide sufficient evidence – in totality – to form the basis of drug approval?
   Would the agency suggest any improvements or other changes in the approach?

FDA Preliminary Response

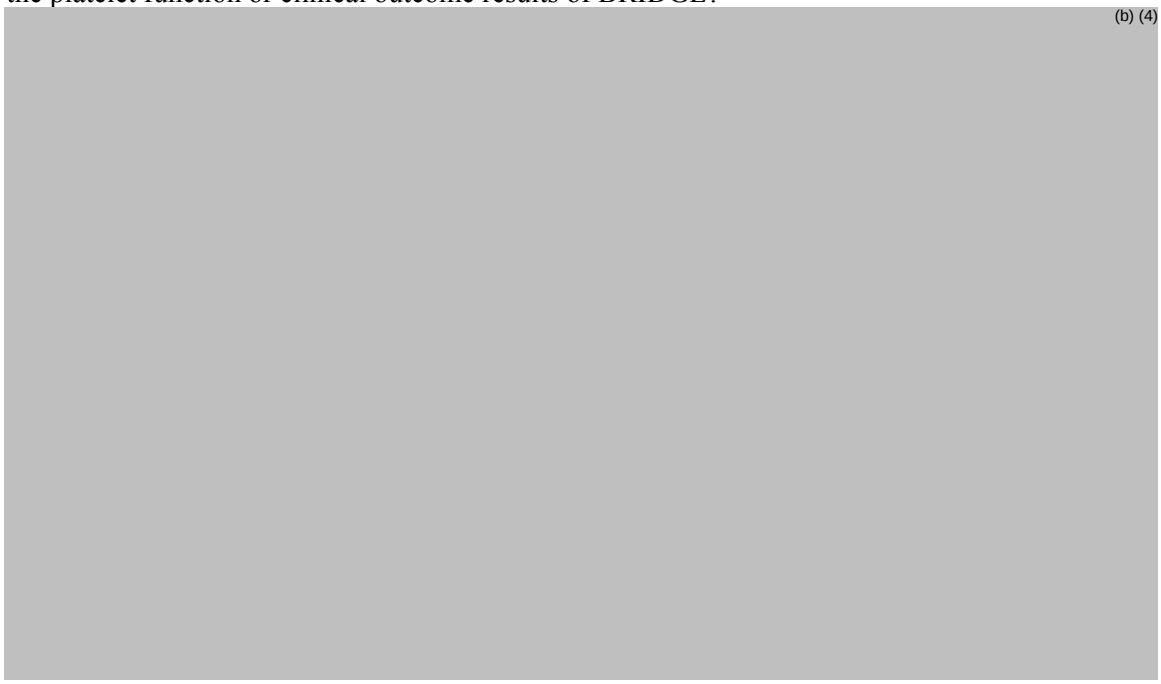
Your question is whether the data from the trials and studies of cangrelor are adequate to result in approval if a NDA is submitted. The available data provide evidence of an effect of cangrelor on platelet function but do not provide documented evidence of clinical benefit (i.e., a reduced rate of

cardiovascular events). The information you provide is not sufficiently detailed for us to reach a conclusion about this question.

We have the following questions and requests for further information:

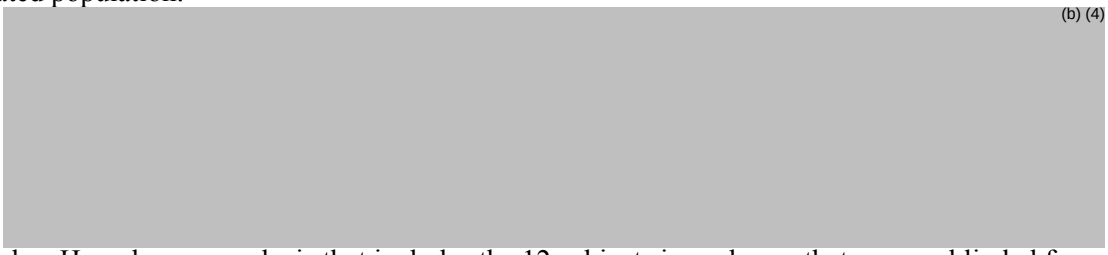
1. You have studied few patients in your intended indication (the "bridging" indication). There were few clinical events and the data do not demonstrate a benefit for cangrelor. There are inadequate clinical outcome data to describe the benefit-risk profile of cangrelor when used in this setting. What methodology do you plan to use in your NDA to assess the benefit-risk profile of cangrelor therapy for the bridging indication?
2. You indicate that investigators were blinded to the results of the VerifyNow P2Y12 test during the study. Might investigators have had access to the results of this test prior to patients being enrolled in BRIDGE?
3. Your final study report should fully describe important baseline characteristics of patients in each analysis population. You should evaluate the implications of imbalances in characteristics on study outcomes. Could the differences (or other factors associated with them) have had an effect on the platelet function or clinical outcome results of BRIDGE?

(b) (4)



4. It appears that your analyses of efficacy in BRIDGE exclude a substantial percentage of randomized patients. For example, your key analysis of platelet function on treatment included 168 subjects, equal to 80% of the 210 subjects randomized and 81% of 207 subjects in the as-treated population.

(b) (4)



   b. How does an analysis that includes the 12 subjects in each arm that were unblinded for the dose-confirmation analysis change the results?

c. Please include patient level analyses of platelet function (% of patients with all on-treatment values less than the PRU cutoff) that include:
    i. All randomized patients (patients with no valid results should be considered PD treatment failures)
    ii. The as-treated safety population (patients with no valid results should be considered PD treatment failures)
d. Table 5 of the briefing package (p. 30) provides information on ischemic endpoints in the safety population. You should also provide analogous data for the complete population of all randomized patients.

5. (b) (4) Do the data from BRIDGE provide adequate information to decide when cangrelor should be initiated and for how long it should be administered prior to surgery? Please provide a rationale for your response.
Your third study of the use of cangrelor in patients undergoing PCI, CHAMPION PHOENIX, is underway. Your two previously completed studies of this use of cangrelor, CHAMPION PCI and CHAMPION PLATFORM, each failed to meet its primary endpoint. If PHOENIX also fails to meet its primary endpoint, would this have any implications for the validity of using platelet function data to establish the effectiveness of cangrelor for the bridging indication? Please provide a rationale for your response.

Discussion at the Meeting

** Trial Execution and Details*

Dr. Meanwell explained that sites in the BRIDGE trial were provided with VerifyNow P2Y12 Test devices whose outputs were masked. The Division asked whether the investigators may have used PRU measurements from unblinded VerifyNow P2Y12 Test devices to decide when to enroll a subject in the trial. The sponsor indicated they did not know.

They explained that to be eligible to enroll, the patient had to be scheduled for CABG and the last dose of thienopyridine could have been administered no more no more than 72 hours prior to randomization (the median was approximately 30 hours). In general, the duration of the infusion during BRIDGE was a function of when CABG was scheduled but the protocol specified that the duration of study drug infusion had to be at least 48 hours.

** Dose*

With regard to the dose chosen for BRIDGE, the sponsor explained that it was chosen based on Phase 2 data. A dose lower than that used in the two completed phase 3 trials was chosen for this study because it was thought that a longer duration of infusion would cause intolerable dyspnea in many subjects, as well as unnecessarily increase the risk of bleeding.

** Point of Care Device (VerifyNow)*

The sponsor explained the VerifyNow P2Y12 Test device was chosen for BRIDGE because was easy to use and the results were reproducible, unlike light transmission aggregometry. The sponsor added that they did not plan to recommend titrating cangrelor dose based on PRU. Dr. Madabushi asked the sponsor to provide platelet aggregation inhibition information for cangrelor and also any information that explored the relationship between platelet aggregation assessed by Light Transmittance Aggregometry and

VerifyNow. The Agency asked the Sponsor to provide the individual time courses for platelet reactivity in the BRIDGE trial and the corresponding data.

Post-Meeting Note:

(b) (4)

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.

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

A follow-up meeting will be scheduled to discuss the information the sponsor has agreed to provide (both those items requested in the preliminary comments and those noted in the action items).

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
1. Provide a list of studies (including the cited observational study) that address the risk of stent thrombosis and other thrombotic events after discontinuation of clopidogrel (Discussion under Question One)	Sponsor	At least three weeks prior to a follow-up meeting
2. Provide a scattergram of PRU values (with means or medians) of the two distinct populations, subjects administered clopidogrel once or a few times for ACS and subjects on chronic clopidogrel for prevention of stent thrombosis (Discussion Under Question One).	Sponsor	At least three weeks prior to a follow-up meeting

3. Explanation for why bridging treatment is needed if few events occur during this time (Discussion Under Question Two).	Sponsor	At least three weeks prior to a follow-up meeting
4. Determine whether investigators had access to VerifyNow prior to enrolling a subject in BRIDGE and if knowledge of results from VerifyNow may have impacted the decision on when to enroll (Discussion Under Question Three).	Sponsor	At least three weeks prior to a follow-up meeting
5. Provide a sensitivity analysis of the difference in PRU in the treatment groups as function of duration of treatment (Post-m=Meeting Proposal Based Upon Discussion Under Question Three).	Sponsor	At least three weeks prior to a follow-up meeting
6. Please provide the necessary data that addresses the potential for rebound in platelet reactivity (Post-Meeting Note Under Question Three).	Sponsor	At least three weeks prior to a follow-up meeting
7. Schedule a follow-up meeting to discuss the sponsor's responses to the Division's questions in the preliminary comments as well as during the meeting.	FDA	Schedule three to four weeks after the sponsor's follow-up document is received.

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/s/

ELLIS F UNGER
06/08/2012

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(781) 464 - 1600
Attention:	Lisa-Sue Wood
Company Name:	The Medicines Company
Phone:	(781) 464 - 1500
Subject:	**Minutes of the Meeting w/FDA, July 6, 2005** IND 56,812
Date:	**August 1, 2005**
Pages including this sheet:	**8**
From:	**Meg Pease-Fye, M.S.**
Phone:	**301-594-5327**
Fax:	**301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

Minutes of a Meeting

Meeting Date:	**July 6, 2005**
Application:	IND 56,812 Cangrelor for Injection
Sponsor:	The Medicines Company
Type of Meeting:	**Type B** **End of Phase 2**
Date requested:	April 18, 2005
Date Confirmed:	April 22, 2005
Date Package Received:	June 13, 2005
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Meg Pease-Fye, M.S.

FDA Participants:
Robert Temple, M.D., Director, Office of Drug Evaluation I, HFD-101
Thomas Marciniak, M.D., Acting Deputy, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical Officers, HFD-110
Shari Targum, M.D., Team Leader, Medical Officers, HFD-110
Albert Defelice, Ph.D., Team Leader, Pharmacology, HFD-110
Robert Kumi, Ph.D., Reviewer, Clinical Pharmacology and Biopharmaceutics, HFD-860
James Hung, Ph.D., Team Leader, Biometrics, HFD-710
Meg Pease-Fye, M.S., Regulatory Health Project Manager, HFD-110

The Medicines Company Participants:
Clive Meanwell, M.D., Ph.D., Chief Executive Officer
John Villiger, Ph.D., Vice President, and Managing Director
Mark Moore-Gillon, Ph.D., Vice President, Product Infrastructure
Kim Carroll, Vice President and General Manager
Christopher Nessel, M.D., Executive Director, Clinical Development
Ping Gao, Ph.D., Senior Director, Biostatistics
Tommy Fu, Ph.D., Associate Director, Biostatistics
James Wong, Ph.D., Director, Clinical Pharmacology
Gary Knappenberger, Senior Director, Regulatory Affairs

Background:
An original IND for this drug, originally developed by AstraZeneca, was received by the Division on January 20, 1998. (b) (4) At that time, the Phase 1 program was complete and ~400 patients had been exposed during Phase 2 studies. The Medicines Company licensed cangrelor in December 2003 (b) (4) The proposed indication for cangrelor is for (b) (4) A meeting with the Division was held on April 14, 2005 to reach agreement regarding the cardiac repolarization assessment needed for cangrelor, specifically the clinical trial

data needed to support cardiac safety. The purpose of this meeting is to discuss the proposed Phase 3 program. TMC has proposed two studies; an active comparator superiority study versus clopidogrel and a placebo-controlled study.

Meeting:
After introductions, Dr. Temple asked TMC to outline the two studies in detail, noting his concern that there was a very short period of time in which cangrelor would be given alone and that once clopidogrel (a drug with similar anti-platelet properties) was given there presumably would be no further benefit of cangrelor. This would seem to mean there would be very few events for cangrelor to prevent. Showing an effect in that circumstance would be a real challenge.

TMC described the **placebo-controlled trial** as a prospective, double-blind trial in patients requiring percutaneous coronary intervention (PCI). Once the intervention is planned, patients could receive aspirin and an anti-thrombotic (unfractionated heparin, bivalirudin, enoxaparin, or other drug that is regionally (U.S., or outside U.S.) appropriate), all prior to randomization to a cangrelor infusion or matching placebo infusion. Randomization could occur either on the way to, or in, the cath lab once there is an expectation that the patient will undergo PCI. TMC noted that the use of glycoprotein IIb/IIIa inhibitors is currently discouraged in the protocol although not prohibited; each site is free to use them. TMC believes that IIb/IIIa inhibitor use is on the decline (used less than 30% of the time) and is being replaced by clopidogrel and bivalirudin adding that use of a IIb/IIIa inhibitor is expected to be less than 10% in this study. Once the procedure is stopped patients will all get clopidogrel.

When TMC was asked what it expects to get out of the proposed study, they responded that it depends on what patient population is being recruited; TMC expects that 10% of the patients will present with non ST elevation myocardial infarction (STEMI) and acute coronary syndrome (ACS).

Dr. Marciniak asked, if over 50% of the patient population has elective PCI (*i.e.* no ACS or STEMI), how does TMC expect to see a large enough event rate. TMC responded that the ESPRIT study, with an event rate of only 10% for eptifibatide was large enough, and expects to be able to detect a 2% risk reduction.

Dr. Temple asked how fast the platelets would return to normal, given cangrelor's physical half-life of less than 5 minutes. TMC responded that they believe this would occur in approximately 20 minutes. TMC will submit the kinetics of cangrelor following IV bolus administration and infusion.

TMC described the **active control trial** as double-dummy. At the time of randomization, the patient will receive an infusion (cangrelor or placebo) and tablets (clopidogrel or placebo). The target patient population is comprised of those at increased risk, presenting with ACS with ischemic ECG changes or abnormal cardiac biomarkers (elevated troponin or creatinine kinase CK-MB). Patients will present with either STEMI or NSTEMI instead of for elective PCI. Dr. Temple remained concerned that there would be very few events occurring during the short period before clopidogrel is active (almost 6 hours) and suggested browsing the Office of Medical Policy (OMP) website for updates on the Agency's thinking about genomics and proteomic predictors of cardiac events. It is possible selecting patients at very high risk would enhance the chances of success. TMC also pointed out that cangrelor's inhibition of platelet function is much more complex than clopidogrel's, a possible advantage even as clopidogrel is becoming active.

TMC said that the drug will be given at the time of randomization, before or during angiography, and that timing will be tracked. Also, all administration of aspirin and thrombolytics, as well as IIb/IIIa inhibitor use, will be at the discretion of the physician. Dr. Targum asked about the use of drug-eluting stents, and TMC noted that they may be used as long as they were approved, and these would also be tracked.

Questions:

Dosing:

1a) TMC has proposed cangrelor dosing as a-30 μg/kg bolus followed by a 4.0 μg/kg/min infusion. Does the Agency have any comments about the proposed dosing?

Discussion: When asked how long they expect the effect to last, TMC responded that they expect to give the drug for about 90 minutes to approximately 3 hours. They do not anticipate dosing to continue for a long period, definitely not as long as 72 hours. TMC does not see the need for extended administration since once there are stents placed, it is anticipated that there will be good laminar flow. All patients in the placebo-controlled trial receive clopidogrel at the time of the procedure, so platelet inhibition is expected by six hours.

Agency response: The Agency finds the proposed dosing acceptable.

1b) In terms of overall exposure, does the Agency agree that exposure in over 5000 patients to a 4.0 μg/kg/min constitutes adequate safety information in support of an NDA approval for cangrelor?

Agency response: The Agency agrees. Dr. Temple noted that Agency will want to see outcome data, especially with any open-label follow-on observations. TMC suggested looking at time to CABG and looking at CABG-related bleeding. It was recommended they submit a formal protocol to the Division for consideration.

Study Design: Active Comparator Trial

2a) Does the Agency concur with the selection of clopidogrel as an active comparator and does the Agency accept that the effect of clopidogrel has been adequately demonstrated in the CURE trial?

Agency response: Clopidogrel appears effective, but the proposed study is a superiority study and if cangrelor is superior in this trial, the documentation of clopidogel's effect is not critical. Dr. Temple noted that possible use of cangrelor is as a substitute for clopidogrel in patients who cannot take tablets, then this could be considered. TMC suggested a scenario of an ACS patient going to CABG, and cannot take clopidogrel. Dr. Temple responded that further conversations can be held to develop fully this idea.

2b) Does the Agency concur with the selection of 300 mg loading dose for clopidogrel, the active comparator?

Agency response: The Agency concurs. In response to the question of when a patient receives clopidogrel, TMC noted that in the placebo-controlled study clopidogrel will be administered immediately post-PCI; six tablets will be used in a bolus.

2c) Is the proposed use of GP IIb/IIIa antagonists at the discretion of physicians acceptable to the Agency?

Agency response: This is acceptable, although IIb/IIa inhibitor use should be tracked.

Study Design: Placebo-Controlled Trial

3a) Does the Agency concur with TMC's plan to conduct the trial at sites where heparin and aspirin are standard-of-care during PCI? TMC recognizes that patients will not receive concomitant treatment with GP IIb/IIIa inhibitors. Is this acceptable to the Agency?

Agency response: Dr. Temple urged TMC to reconsider the exclusion of GP IIb/IIIa inhibitors, noting recent criticism of the ESPRIT trial.

3b) Does the Agency concur with TMC's plan to give all patients clopidogrel after the index PCI, provided a contraindication is absent?

Agency response: The Agency concurs.

Statistics: Non-inferiority and Associated Issues

4a) The primary efficacy variable for both trials will be the composite incidence of all-cause mortality, non-fatal myocardial infarction and ischemia-driven revascularization during the first 48 hours after randomization for the ITT population. Does the Agency concur with the use of this endpoint?

Agency response: The Agency concurs.

4b) Both studies contemplate group sequential testing upon compilation of 48 hour outcome data at pre-specified intervals. The O'Brien-Fleming alpha spending function will be employed. Sample size re-estimation will be performed based on observed event rates per group during each of the interim analyses. Rules for early termination of the trial will be defined by the executive committee and DSMB. Assuming normal standards of blinding, data processing and data confidentiality are successfully maintained by the DSMB and Sponsor, does the Agency concur with this plan?

Agency response: Dr. Hung asked if TMC planned on a sample size adjustment based on observed event rate, stating that a rationale would need to be provided. TMC stated that this was still under consideration. Dr. Hung noted that if the observed difference in event rate between Treatment A versus Treatment B is used at an interim analysis to increase sample size, the protocol will need to provide details of how α will be adjusted. It was strongly recommended that TMC work out the details, and submit a Special Protocol Assessment to the Division for comment.

Definitions of Clinical Endpoints

5a) For both trials, non-fatal MI after PCI is defined as, "…CK-MB ≥3x ULN and >50% above the value prior to the procedure or new Q-waves (≥0.04 s duration) in at least two contiguous leads." Does the Agency concur with the use of this definition on non-fatal MI?

Agency response: The Agency concurs.

5b) For both trials, ischemic-driven revascularization is defined as, "…one or more episodes of rest pain, presumed to be ischemic in origin, which result in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST-segment changes indicative of ischemia, acute pulmonary edema, ventricular arrhythmias or hemodynamic instability presumed to be ischemic in origin will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will generally be initiated within 24 hours of the last episode of ischemia. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guidewire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, will also be considered an ischemia-driven revascularization endpoint." Does the Agency concur with this definition of ischemia-driven revascularization?

Agency response: The Agency concurs.

5c) For both trials, hemorrhages will be classified by the GUSTO criteria. The criteria are as follows: "Hemorrhage will be classified as, moderate or severe/life-threatening. Bleeding will be classified as mild if no transfusion or hemodynamic compromise results; moderate, if transfusion is required; or severe/life-threatening, if it is intracranial hemorrhage or if hemodynamic compromise results." Minor and other bleeding will be reported as well. Bleeding events will be captured for 48 hours after cessation of study drug or until hospital discharge, whichever occurs first. Does the Agency concur with this plan?

Agency response: The Agency concurs.

Proposed Indication

The proposed indication for cangrelor is, "(b) (4) Does the Agency concur that this program, if successfully executed, will support approval for this indication?

Agency response: The Agency did not think the proposed indication would prove acceptable. First, the indication is clearly linked to PCI, (b) (4). Second, it is overwhelmingly likely that any effect will be on acute MI and revascularization, (b) (4) TMC asked if (b) (4). Dr. Temple responded that, no, the studies would not support such a broader claim.

TMC asked if prevention of platelet aggregation is a surrogate endpoint. They believe that if they can demonstrate chronic inhibition of platelet aggregation is beneficial, this can be determined in patients not adequately controlled at the time of PCI. Further, they believe that cangrelor's advantage is that it can inhibit platelets in a controlled fashion. The Agency said it was not ready to accept this, although, as noted earlier, we would consider the possibility that cangrelor could provide clopidogrel-like platelet inhibition in patients who cannot take oral medications.

Other Discussion Points:

- Dr. Temple recommended TMC monitor placental growth factor and CD-40 ligand levels, referring to an article (JAMA 2004 Jan 28,291(4):435-41) by the CAPTURE trial investigators and consider for the elective study (placebo-controlled), selecting patients with elevated placental growth factor and CD-40 ligand, which could lead to more events and a much smaller study. Even if all patients had to be included in the study because measurements would not be available, it would be possible to identify as the primary study population people with elevated levels of placental growth factor, CD-40 ligand, and troponin (already being measured). Further discussion is recommended to work out the statistical details

Conclusions:

- TMC will submit the kinetics of the bolus and infusion
- TMC will track the following
    - GP IIb/IIa use
    - stent placement
    - when drug is administered

Date Minutes Drafted: July 12, 2005
Date Minutes Finalized: August 1, 2005

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

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

Reviewed:

R. Temple	8.01.05
T. Marciniak	7/15/05
A. Karkowsky	7/14/05
S. Targum	7/14/05
A. Defelice	7/12/05
R. Kumi	7/14/05
J. Hung	7/13/05

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

/s/

Margaret Pease-Fye
8/1/05 01:38:33 PM

Robert Temple
8/4/05 05:24:05 PM

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

LATE-CYCLE MEETING MINUTES

The Medicines Company
ATTENTION: Stephen Sherman, JD, M.B.A.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on 29 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.
Cross-Discipline 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

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: 29 January 2014 from 1030- 1200
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903
Application Number: NDA 204958
Product Name: cangrelor for injection
Proposed Indication: **PCI**

Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

Bridging

Cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

Applicant Name: The Medicines Company
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
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Clinical Reviewer
Fortunato Senatore, M.D., Ph.D.	Clinical Reviewer
Nhi Beasley, PharmD	Clinical Reviewer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology/Toxicology
Belay Tesfamariam, Ph.D.	Pharmacology/Toxicology Reviewer
Ed Fromm, RPh, RAC	Chief Regulatory Project Manager
Alison Blaus, RAC	Regulatory Health Project Manager

* *Office of Clinical Pharmacology*	
Sreedharan Sabarinath, Ph.D.	Reviewer
* *Office of Biostatistics*	
Jialu Zhang, Ph.D.	Statistician
* *Office of Surveillance and Epidemiology*	
Kimberly Lehrfield, PharmD	DRISK Team Leader
Somya Dunn, M.D.	DRISK Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Patrick J. Zhou	Independent Assessor

APPLICANT ATTENDEES

Clive Meanwell, M.D.	CEO
Simona Skerjanec, Pharm.D.	Product Development
Jonathan Day, M.D., Ph.D.	Medical Director
Jayne Prats, Ph.D.	Clinical Pharmacology
Tiepu Liu , M.D., Ph.D.	Statistics
Efthymios N. Deliargyris, M.D.	Clinical
(b) (4)	
Steve Sherman, J.D.	Global Regulatory Affairs

1.0 BACKGROUND

NDA 204958 was submitted on 30 April 2013 for cangrelor for injection.
Proposed indications: **PCI**

Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

Bridging

Cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

PDUFA goal date: 30April 2014
FDA issued a Background Package in preparation for this meeting on 21 January 2014.

2.0 DISCUSSION

1. *Discussion of Substantive Review*
   The following substantive review issues have been identified to date:

   Biostatistics
   - There was an imbalance on the actual loading dose between the two treatment groups. The clopidogrel patients taking 300 mg loading dose appeared to have a higher event rate than those taking 600 mg loading dose in both 48 hour primary endpoint and 30 day composite event. Although the treatment effect of cangrelor was still trending in the right direction when compared with clopidogrel patients who had 600 mg loading dose, the results favoring cangrelor seemed to be driven by the comparison with the patients given 300 mg clopidogrel loading dose.

   Medical
   - The ethics of delaying clopidogrel administration
   - The effects of delaying clopidogrel administration on the endpoints
   - The interpretation of comparing cangrelor to clopidogrel used differently than in its trials supporting approval
   - The effects of specifying clopidogrel 600 mg loading in the cangrelor arm but allowing 300 mg and 600 mg in the clopidogrel arm
   - The possibility of harm with cangrelor for STEMI
   - The benefit predominantly for periprocedural MIs and IPST with no significant benefit for a composite endpoint based on site-reported event
   - The increased risk of bleeding with the cangrelor regimen
   - The benefit-risk of cangrelor considering all of the above
   - Possible underreporting of events at 30 days in PHOENIX
   - The effect of combining the original clinically correlated defined stent thrombosis endpoint (ARC-ST), with an angiographic image parameter (IPST) and subsequently re-defining the ST component of the primary endpoint.
   - The applicability of the Dutch Stent Thrombosis Registry to the BRIDGE to CABG population described in the BRIDGE trial
   - The quality and consistency of the published literature used to support the argument that oral P2Y12 therapy too close to CABG will increase the risk of bleeding during CABG
   - The approval for an indication with only PD data in the setting where published studies failed to show a difference in clinical outcome between two oral P2Y12 doses providing a dose-dependent difference in platelet reactivity

Discussion during the Meeting

PCI Indication

Dr. Marciniak opened the conversation to note that by looking at the primary endpoint alone, the Agency agreed that the PHOENIX trial was successful. The critical questions that remain are whether the procedures applied in this trial are similar to standard of care, whether cangrelor was superior to clopidogrel used correctly (i.e., the way it was administered in some of the clopidogrel registration trials [i.e., CURE]), and whether some acute coronary syndrome (ACS) subgroups should be excluded based on the PHOENIX results (i.e., ST elevation myocardial infarction [STEMI] patients). The Division asked whether with the approval of prasugrel and, later, ticagrelor, the protocol should have been amended to allow for their use since both were shown to have superior efficacy to clopidogrel in ACS patients.

The Applicant asked the Division to expand on the "Ethicalness of the Cangrelor Development Program" review in the AC briefing book. Dr. Marciniak, as the reviewer who expressed this concern in this review, reiterated his belief that the program utilized less than optimal delivery of clopidogrel and that communications from TMC indicated that clopidogrel would be given at the start of angioplasty (the protocol stated that clopidogrel should be administered "as soon as possible after randomization,"), but that did not reflect the way clopidogrel was actually given, which was often later than that. Dr. Marciniak also expressed the view that in in light of the CHAMPION-PLATFORM data, still earlier (pre-angioplasty) administration of clopidogrel should have been allowed. The applicant voiced disagreement with the Division's conclusions and accusations, citing various recommendations in guidance from cardiology groups. The applicant requested that since the statement on page 301 of the briefing book (page 34 of the review) stating, [redacted] did not add to the scientific discussion of the application at the advisory committee, and was highly debatable, that it be redacted from the book to be available to the public. Although Dr. Marciniak agreed to have this statement redacted from his review, the Agency explained that they needed to discuss the matter further internally and would let the applicant know if this was appropriate and feasible.

Dr. Temple asked the sponsor why the loading dose of clopidogrel for the clopidogrel arm was left to investigator discretion (300 or 600 mg) while the loading dose for the cangrelor arm was stipulated in the protocol to be 600 mg. TMC explained that the rationale was based on clinical pharmacology, specifically, when clopidogrel was administered with some cangrelor still meant the effect of clopidogrel would be diminished. Dr. Marciniak noted, in general, when investigators used the 300mg clopidogrel loading dose it tended to be given earlier.

BRIDGE Indication
Dr. Temple noted that the approvability of BRIDGE does not hinge on the PCI indication and that the PHOENIX data provide affirmation of the drug's pharmacodynamic (PD) effect, although at a higher dose. The BRIDGE indication, however, is a debatable topic because the dose was lower and there was not a large database. Dr. Senatore echoed this concern.

2. *Discussion of Upcoming Advisory Committee Meeting*

Discussion during the Meeting
Dr. Temple said that TMC needs to make the case at the Advisory Committee that the treatment in PHOENIX was compatible with current practice (standard of care). Dr. Temple added that TMC needs to be ready to answer ethical related questions and that it would be advisable to have an ethicist on their side to answer questions.

3. *Major labeling issues*

Microbiology

- The conclusions of the growth promotion study of the reconstituted and diluted product, submitted on 10/09/2013, are not reflected in product labeling. (b) (4) [redacted] the growth promotion study concludes that product diluted in 5% Dextrose may be stored at room temperature for only 12 hours. The suggested storage period for product diluted in Sodium Chloride for Injection, at 24 hours, is supported by

the study and is acceptable. Please amend the product labeling to (b) (4) the storage period for the reconstituted drug product, diluted in 5% Dextrose to 12 hours at room temperature.

Medical

- Effects on renal function section, page 9 of the USPI. Please clarify if that information is displayed (b) (4)?
- Hypersensitivity section, page 9 of the USPI. Please clarify if that data is displayed (b) (4)?

Discussion during the Meeting
No further discussion.

4. *Review Plans*

Discussion during the Meeting
No further discussion.

5. *Wrap-up and Action Items*

Discussion during the Meeting
The Agency agreed to discuss further internally and to follow-up with the Advisory Committee staff regarding the possibility of redacting the sentence discussed in Section 1 of these minutes.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

ALISON L BLAUS
02/27/2014

THOMAS A MARCINIAK
02/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204958

LATE CYCLE MEETING
BACKGROUND PACKAGE

The Medicines Company
ATTENTION: Stephen Sherman, Ph.D.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Sherman:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for 29 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:	29 January 2014 from 1030- 1200
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 204958
Product Name:	cangrelor for injection
Proposed Indication:	**PCI** Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)]. **Bridging** Cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].
Applicant Name:	The Medicines Company

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

- There was an imbalance on the actual loading dose between the two treatment groups. The clopidogrel patients taking 300 mg loading dose appeared to have a higher event rate than those taking 600 mg loading dose in both 48 hour primary endpoint and 30 day composite event. Although the treatment effect of cangrelor was still trending in the right direction when compared with clopidogrel patients who had 600 mg loading dose, the results favoring congrelor seemed to be driven by the comparison with the patients given 300 mg clopidogrel loading dose.

Medical

- The ethics of delaying clopidogrel administration
- The effects of delaying clopidogrel administration on the endpoints
- The interpretation of comparing cangrelor to clopidogrel used differently than in its trials supporting approval
- The effects of specifying clopidogrel 600 mg loading in the cangrelor arm but allowing 300 mg and 600 mg in the clopidogrel arm
- The possibility of harm with cangrelor for STEMI
- The benefit predominantly for periprocedural MIs and IPST with no significant benefit for a composite endpoint based on site-reported event
- The increased risk of bleeding with the cangrelor regimen
- The benefit-risk of cangrelor considering all of the above
- Possible underreporting of events at 30 days in PHOENIX
- The effect of combining the original clinically correlated defined stent thrombosis endpoint (ARC-ST), with an angiographic image parameter (IPST) and subsequently re-defining the ST component of the primary endpoint.
- The applicability of the Dutch Stent Thrombosis Registry to the BRIDGE to CABG population described in the BRIDGE trial
- The quality and consistency of the published literature used to support the argument that oral P2Y12 therapy too close to CABG will increase the risk of bleeding during CABG
- [redacted] (b) (4)

3. Major Labeling Issues

Microbiology

- The conclusions of the growth promotion study of the reconstituted and diluted product, submitted on 10/09/2013, are not reflected in product labeling. [redacted] (b) (4) the growth promotion study concludes that product diluted in 5% Dextrose may be stored at room temperature for only 12 hours. The suggested storage period for product diluted in Sodium Chloride for Injection, at 24 hours, is supported by the study and is acceptable. Please amend the product labeling to [redacted] (b) (4) the storage period for the reconstituted drug product, diluted in 5% Dextrose to 12 hours at room temperature.

Medical

- Effects on renal function section, page 9 of the USPI. Please clarify if that information is displayed [redacted] (b) (4)?
- Hypersensitivity section, page 9 of the USPI. Please clarify if that data is displayed [redacted] (b) (4)?

4. Advisory Committee Meeting

Date of AC meeting: 12 February 2014

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: 23 January 2014

Potential questions and discussion topics for AC Meeting are as follows:

1. The CHAMPION studies demonstrated that delaying clopidogrel administration is hazardous to the patient. In PLATFORM, in which clopidogrel administration was delayed until after PCI, deaths and stent thromboses were significantly greater in the clopidogrel arm. The odds ratios of the efficacy endpoints in all three trials are approximately directly proportional to the median timings of clopidogrel administration relative to start of PCI. Logistic regressions of clopidogrel timing data in PHOENIX suggest that earlier administration is associated with better efficacy.
   a. How convincing do you find the CHAMPION program evidence regarding the hazards of delaying clopidogrel administration?
   b. The clopidogrel label does not include specific directions regarding the timing of initiating clopidogrel relative to PCI although it the clopidogrel trials drug was given immediately after randomization without delay.
      i. [redacted] (b) (4)
      ii.
      iii.
      iv.
      v.

(b) (4)

2. The FDA analyses of clopidogrel timings in the CHAMPION program suggest that if clopidogrel had been administered universally prior to PCI in the clopidogrel arm, the cangrelor regimen would not show superiority to the clopidogrel regimen.

   a. Do you consider the clopidogrel timing data sufficiently persuasive to deny an efficacy superiority claim for cangrelor based on them alone?

   b. Can you propose other analyses to elucidate this issue?

   c. Is an additional study or studies needed to address this issue?

3. The primary endpoint rate at 48 hours in the stable angina subgroup of PHOENIX was about 6 percent. The predominant components of this primary endpoint were type 4a periprocedural MIs documented by biomarker increases. Some experts have questioned the clinical utility of the biomarker increases specified in the universal definition of MI (UDMI).

   a. Do you consider the UDMI biomarker specifications to be optimal for judging the efficacy of a drug?

   b. If not, what specifications do you prefer?

   c. How should the UDMI type 4a MIs based on small biomarker increases be handled in evaluating the benefit-risk of a drug?

4. Interpretations differ regarding whether the cangrelor regimen showed superior efficacy to the clopidogrel regimen but the cangrelor regimen clearly produced more bleeding.

   a. What is the best way to evaluate the benefit-risk of cangrelor?

   b. What is your evaluation of the benefit-risk?

5. The major subgroup in the successful PHOENIX trial was the stable angina subgroup. There is some evidence of harm in the STEMI subgroup with the cangrelor regimen in PHOENIX and no evidence of benefit in PCI. The data for UA/NSTEMI are equivocal regarding benefit.

   a. How persuasive do you find the STEMI data?

   b. Is an additional study or studies needed to address this issue for cangrelor?

   c. Should the FDA insist upon sponsors' adequately sizing studies or performing separate studies of antiplatelet drugs for STEMI, UA/NSTEMI, and stable angina subgroups?

6. The cangrelor outcome trials prohibited the use of ticagrelor and prasugrel prior to the 48 hour endpoint evaluation. PHOENIX also prohibited the use of glycoprotein IIb/IIIa inhibitors (GPIs) except for bailout use.

   a. Because both prasugrel and ticagrelor have evidence of superior effects on death and irreversible harm compared to clopidogrel, should the FDA insist upon new agents being compared to the more effective agents?

   b. Should the FDA insist that GPIs be allowed in new antiplatelet trials?

   c. Is an additional study or studies needed to address these issues for cangrelor?

7. An FDA review has raised the issue of whether the conduct of the cangrelor development program was unethical because of the delays in clopidogrel dosing; the prohibition on prasugrel,

ticagrelor, and GPIs; and the applicant's failure to communicate these issues and the PLATFORM results to the FDA, the sites, the IRBs, and the subjects.

a. How serious do you consider these alleged ethical violations?

b. Do you recommend any actions regarding them?

8. Do you recommend approval of the PCI indication without any restrictions?

   a. If not, do you recommend approval of the PCI indication with restrictions? Specify the restrictions.

   b. If you do not recommend approval at this time, what studies do you recommend that would lead to approval?

Regarding the BRIDGE indication:

9. The justification for the bridging indication is based solely on pharmacodynamic data.

   a. Do you consider this justification reasonable?

   b. In what situations should the FDA accept pharmacodynamic justifications?

10. BRIDGE relied upon platelet reactivity unit (PRU) as measured by the VerifyNow® P2Y12 assay. Several studies (GRAVITAS {Price et al, 2011, JAMA, 305(11):1097-1105}, TRIGGER-PCI {Trenk et al, 2012, JACC, 59(24):2159-2164}, and ARCTIC {Collet et al, 2012, NEJM, 367:2100-2109}) have failed to show a correlation between PRU and clinical outcome.

    a. Given these findings, how reliable is PRU data as a prognostic indicator of clinical events to warrant approval of a bridging indication?

    b. Does BRIDGE validate the dosing used as predictive of a positive benefit-risk such that a clinical trial characterizing benefits and risks is not needed?

11. The applicant has relied on the Dutch Stent Registry study as the basis for justifying the BRIDGE indication. The Registry showed that cessation of clopidogrel was a prognostic indicator for stent thrombosis. The original publication evaluated the temporal relationship between discontinuation of clopidogrel and stent thrombosis using the model "cessation of clopidogrel within 14 days before stent thrombosis" as a time-varying covariate. The results of this evaluation showed that the prognostic strength was highest in the initial 30 days from the index PCI, but there was insufficient data to draw a conclusion when the time from index PCI to stent thrombosis exceeded 6 months. The applicant performed their own analysis and concluded from the same database that the risk of stent thrombosis within 7 days from discontinuing clopidogrel was independent of the time between index PCI and stent thrombosis (ST). Their analysis was based on three PCI→ST time-period groupings: < 30 days, < 180 days, and < 365 days. The data from the registry showed that 73% of the patients had a ST within 30 days from index PCI following cessation of clopidogrel within 14 days before ST. Therefore, it was felt that the applicant's analysis was impacted by the <30 days group. Approximately 50% of the BRIDGE patients underwent stent deployment, and the majority of these stented patients received their stent in excess of 6 months prior to CABG. Given these findings:

    a. Is the Dutch Stent Thrombosis registry applicable to the BRIDGE population?

b. Is the applicant's conclusion that the risk of stent thrombosis within 7 days of discontinuing clopidogrel is independent of the time between index PCI and stent thrombosis reasonable and justified?

c. Are the findings from the Dutch Stent Thrombosis Registry sufficiently strong to warrant a bridging indication?

12. The applicant presented two meta-analyses and one review to support the argument that termination of clopidogrel too close to CABG would cause bleeding adverse events during CABG. Furthermore, the guidelines and warning labels of approved $P2Y_{12}$ inhibitors provide for discontinuation of such therapy 5-7 days prior to CABG. One of the meta-analyses (Biancari et al, 2012, J. Thorac Cardiovasc Surg, 143:665-675) involved post-hoc studies from three megatrials (CLARITY, CREDO, CAPRIE) and 17 observational studies evaluating the benefit and risk of clopidogrel before CABG. The conclusion was that the post-hoc studies showed benefit in contrary to the observational studies. In the other meta-analysis (Nijjer et al, 2011, Circ, 116:2544-2552), the risk of continuing clopidogrel during the 5-7 days prior to CABG was evaluated in 22,584 patients in 34 studies. The conclusion was that patients have safely undergone CABG on clopidogrel and surgical expertise is growing (e.g. on how to manage antiplatelet activity during CABG). Finally, in a review of 37 studies (Au, et al, 2012, AM J Med, 125:87-99), the exposure to clopidogrel within 5 days before CABG, vs. no exposure, was evaluated in order to address the influence of pre-operative thienopyridine administration within the 5 day timeframe on the 30-day post-operative outcome. The review showed no effect on post-op MI (23 studies), increased risk of stroke (16 studies), increased risk of reoperation for bleeding (32 studies) and an increased risk of all-cause mortality (28 studies). The conclusion was that withholding thienopyridine therapy 5 days before CABG was supported by the results of the review.

    a. Given the mixed results of these meta-analyses and review, is the evidence provided by the applicant that the risk of bleeding due to discontinuation of thienopyridine therapy too close to CABG sufficiently strong to warrant a bridging indication?

13. Do you recommend approval of the bridging indication?

    a. If not, what studies do you recommend that would lead to approval?

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

5. 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 – 50 minutes
    - Each issue will be introduced by FDA and followed by a discussion.
3. Discussion of Upcoming Advisory Committee Meeting – 15 minutes (ALL)
    - Discussion of general content of presentations to eliminate potential overlap in Applicant vs. Agency presentations.
4. Major labeling issues – 10 minutes
5. Review Plans – 5 minutes (FDA)
    - The review team will briefly discuss those items of the application that are still pending review.
6. Wrap-up and Action Items – 5 minutes (RPM)

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

/s/

ALISON L BLAUS
01/21/2014

NORMAN L STOCKBRIDGE
01/21/2014