

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206143Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**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

206143

NAME OF APPLICANT/NDA HOLDER

Amgen Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Corlanor

ACTIVE INGREDIENT(S)

ivabradine hydrochloride (see attached sheet)

STRENGTH(S)

5 mg and 7.5 mg (free base equivalent)  
5.39 mg and 8.085 mg (ivabradine hydrochloride)

DOSAGE FORM

oral tablet

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

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

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

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

**1. GENERAL**

a. United States Patent Number 7,361,649	b. Issue Date of Patent 04/22/2008	c. Expiration Date of Patent 04/17/2026
d. Name of Patent Owner Les Laboratoires Servier	Address (of Patent Owner) 35 rue de Verdun	
	City/State Suresnes, Cedex	
	ZIP Code France	FAX Number (if available) 0033 1 55 72 57 72
	Telephone Number 0033 1 55 72 60 00	E-Mail Address (if available) mail.patent12-def@fr.netgrs.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.85 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Stuart Watt Amgen Inc.	Address (of agent or representative named in f.e.) One Amgen Center Drive	
	City/State Thousand Oaks, CA	
	ZIP Code 91320-1799	FAX Number (if available) (805) 499-8011
	Telephone Number (805) 447-2154	E-Mail Address (if available) swatt@amgen.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes <input type="checkbox"/> No	

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 314.63(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:

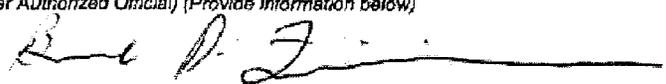
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 5 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.)  
 TRADENAME (ivabradine) is indicated to reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in patients with chronic heart failure NYHA Class II to IV with systolic dysfunction and in sinus rhythm with heart rate  $\geq$  70 beats per minute (bpm), in combination with standard therapy including maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated or not tolerated.

**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	
<p>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.</p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>04/30/2014</p>
<p><b>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).</b></p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Bernard P. Friedrichsen, Senior Counsel</p>	
<p>Address</p> <p>One Amgen Center Drive</p>	<p>City/State</p> <p>Thousand Oaks, CA</p>
<p>ZIP Code</p> <p>91320-1799</p>	<p>Telephone Number</p> <p>(805) 447-0628</p>
<p>FAX Number (if available)</p> <p>(805) 499-8011</p>	<p>E-Mail Address (if available)</p> <p>bernardf@amgen.com</p>
<p>This section applies only to requirements of the Paperwork Reduction Act of 1995.</p> <p><b>*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*</b></p> <p>The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:</p> <p style="text-align: center;">             Department of Health and Human Services              Food and Drug Administration              Office of Chief Information Officer              Paperwork Reduction Act (PRA) Staff              PRAStaff@fda.hhs.gov           </p> <p style="text-align: center;"> <i>"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 number."</i> </p>	

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

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

**First Section**

Complete all items in this section.

**1. General Section**

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

- 1e) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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

**2. Drug Substance (Active Ingredient)**

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

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

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

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

**4. Method of Use**

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

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

# Attached Sheet for Form 3542a

## US Patent No. 7,361,649

An application for a United States Adopted Name (USAN) was filed in December of 2013, to obtain approval of the generic names ivabradine and ivabradine hydrochloride. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine dated April 29, 2014, has now been received. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine hydrochloride dated April 30, 2014, has also now been received.

Ivabradine has been approved as an International Nonproprietary Name (INN) by the World Health Organization (WHO). The INN number is 7523.

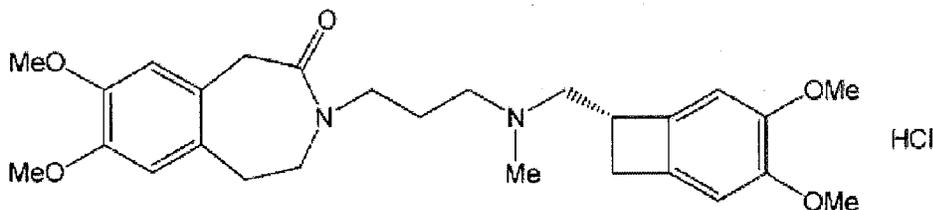
The Chemical Abstract Service (CAS) Registry Number for the hydrochloride salt form is 148849-67-6. The CAS Registry Number for the base form is 155974-00-8. The CA Index Name for the hydrochloride salt is provided below

2H-3-Benzazepin-2-one, 3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-, hydrochloride (1:1).

A synonym for this name is provided below.

3-(3-[[[(7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino]propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride

The structure of the compound is shown below.



**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

206143

NAME OF APPLICANT/NDA HOLDER

Amgen Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Corlanor

ACTIVE INGREDIENT(S)

ivabradine hydrochloride (see attached sheet)

STRENGTH(S)

5 mg and 7.5 mg (free base equivalent)  
5.39 mg and 8.085 mg (ivabradine hydrochloride)

DOSAGE FORM

oral tablet

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

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

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

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

**1. GENERAL**

a. United States Patent Number

7,361,650

b. Issue Date of Patent

04/22/2008

c. Expiration Date of Patent

04/14/2026

d. Name of Patent Owner

Les Laboratoires Servier

Address (of Patent Owner)

35 rue de Verdun

City/State

Suresnes, Cedex

ZIP Code

France

FAX Number (if available)

0033 1 55 72 57 72

Telephone Number

0033 1 55 72 60 00

E-Mail Address (if available)

mail.patent12-def@fr.netgrs.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Stuart Watt  
Amgen Inc.

Address (of agent or representative named in 1.e.)

One Amgen Center Drive

City/State

Thousand Oaks, CA

ZIP Code

91320-1799

FAX Number (if available)

(805) 499-8011

Telephone Number

(805) 447-2154

E-Mail Address (if available)

swatt@amgen.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes  No

**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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
5		

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.) TRADENAME (ivabradine) is indicated to reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in patients with chronic heart failure NYHA Class II to IV with systolic dysfunction and in sinus rhythm with heart rate $\geq$ 70 beats per minute (bpm), in combination with standard therapy including maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated or not tolerated.
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**5. No Relevant Patents**

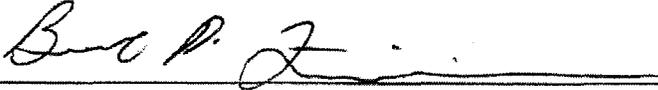
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably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

04/30/2014

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.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Bernard P. Friedrichsen, Senior Counsel	
Address One Amgen Center Drive	City/State Thousand Oaks, CA
ZIP Code 91320-1799	Telephone Number (805) 447-0628
FAX Number (if available) (805) 499-8011	E-Mail Address (if available) bernardf@amgen.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.  
**\*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.\***

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services  
 Food and Drug Administration  
 Office of Chief Information Officer  
 Paperwork Reduction Act (PRA) Staff  
 PRAStaff@fda.hhs.gov

*"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 number."*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

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

**First Section**

Complete all items in this section.

**1. General Section**

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

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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

**2. Drug Substance (Active Ingredient)**

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

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

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

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

**4. Method of Use**

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

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

# Attached Sheet for Form 3542a US Patent No. 7,361,650

An application for a United States Adopted Name (USAN) was filed in December of 2013, to obtain approval of the generic names ivabradine and ivabradine hydrochloride. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine dated April 29, 2014, has now been received. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine hydrochloride dated April 30, 2014, has also now been received.

Ivabradine has been approved as an International Nonproprietary Name (INN) by the World Health Organization (WHO). The INN number is 7523.

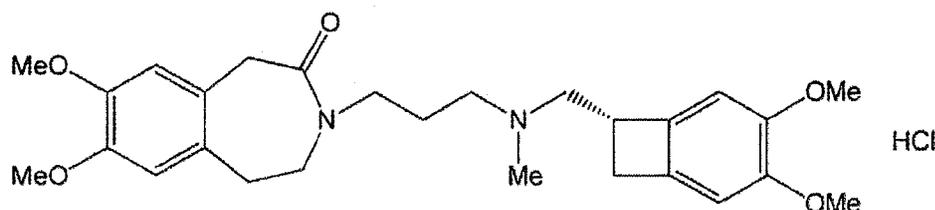
The Chemical Abstract Service (CAS) Registry Number for the hydrochloride salt form is 148849-67-6. The CAS Registry Number for the base form is 155974-00-8. The CA Index Name for the hydrochloride salt is provided below

2H-3-Benzazepin-2-one, 3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-, hydrochloride (1:1).

A synonym for this name is provided below.

3-(3-[[[(7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride

The structure of the compound is shown below.



**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

206143

NAME OF APPLICANT/NDA HOLDER

Amgen Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Corlanor

ACTIVE INGREDIENT(S)

ivabradine hydrochloride (see attached sheet)

STRENGTH(S)

5 mg and 7.5 mg (free base equivalent)  
5.39 mg and 8.085 mg (ivabradine hydrochloride)

DOSAGE FORM

oral tablet

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)(i) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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

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

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

**1. GENERAL**

a. United States Patent Number 7,867,996	b. Issue Date of Patent 01/11/2011	c. Expiration Date of Patent 02/22/2026
d. Name of Patent Owner Les Laboratoires Servier	Address (of Patent Owner) 35 rue de Verdun	
	City/State Suresnes, Cedex	
	ZIP Code France	FAX Number (if available) 0033 1 55 72 57 72
	Telephone Number 0033 1 55 72 60 00	E-Mail Address (if available) mail.patent12-def@fr.netgrs.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Stuart Watt Amgen Inc.	Address (of agent or representative named in 1.e.) One Amgen Center Drive	
	City/State Thousand Oaks, CA	
	ZIP Code 91320-1799	FAX Number (if available) (805) 499-8011
	Telephone Number (805) 447-2154	E-Mail Address (if available) swatt@amgen.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

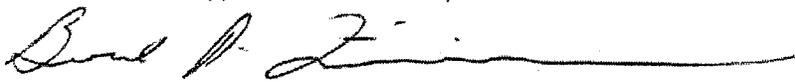
**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	
4, 6	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) TRADENAME (ivabradine) is indicated to reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in patients with chronic heart failure NYHA Class II to IV with systolic dysfunction and in sinus rhythm with heart rate $\geq 70$ beats per minute (bpm), in combination with standard therapy including maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated or not tolerated.
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**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.	<input type="checkbox"/> Yes
---	------------------------------

6. Declaration Certification	
<p>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.</p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>04/30/2014</p>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Bernard P. Friedrichsen, Senior Counsel</p>	
<p>Address</p> <p>One Amgen Center Drive</p>	<p>City/State</p> <p>Thousand Oaks, CA</p>
<p>ZIP Code</p> <p>91320-1799</p>	<p>Telephone Number</p> <p>(805) 447-0628</p>
<p>FAX Number (if available)</p> <p>(805) 499-8011</p>	<p>E-Mail Address (if available)</p> <p>bernardf@amgen.com</p>
<p>This section applies only to requirements of the Paperwork Reduction Act of 1995.</p> <p><b>*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*</b></p> <p>The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:</p> <p style="text-align: center;">             Department of Health and Human Services              Food and Drug Administration              Office of Chief Information Officer              Paperwork Reduction Act (PRA) Staff              PRAStaff@fda.hhs.gov           </p> <p style="text-align: center;"><i>"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 number."</i></p>	

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

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

**First Section**

Complete all items in this section.

**1. General Section**

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

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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

**2. Drug Substance (Active Ingredient)**

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

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

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

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

**4. Method of Use**

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

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

# Attached Sheet for Form 3542a US Patent No. 7,867,996

An application for a United States Adopted Name (USAN) was filed in December of 2013, to obtain approval of the generic names ivabradine and ivabradine hydrochloride. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine dated April 29, 2014, has now been received. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine hydrochloride dated April 30, 2014, has also now been received.

Ivabradine has been approved as an International Nonproprietary Name (INN) by the World Health Organization (WHO). The INN number is 7523.

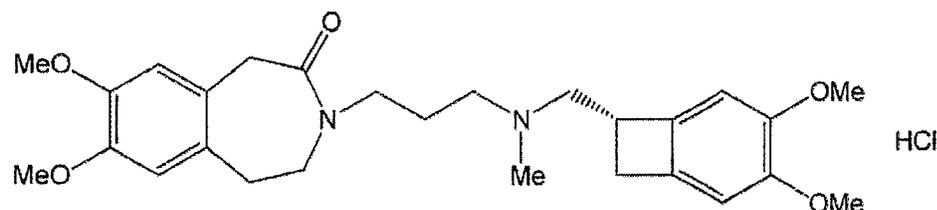
The Chemical Abstract Service (CAS) Registry Number for the hydrochloride salt form is 148849-67-6. The CAS Registry Number for the base form is 155974-00-8. The CA Index Name for the hydrochloride salt is provided below

2H-3-Benzazepin-2-one, 3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-, hydrochloride (1:1).

A synonym for this name is provided below.

3-(3-[[[(7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino]propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride

The structure of the compound is shown below.



**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

206143

NAME OF APPLICANT/NDA HOLDER

Amgen Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Corlanor

ACTIVE INGREDIENT(S)

ivabradine hydrochloride (see attached sheet)

STRENGTH(S)

5 mg and 7.5 mg (free base equivalent)  
5.39 mg and 8.085 mg (ivabradine hydrochloride)

DOSAGE FORM

oral tablet

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)(i) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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

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

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

**1. GENERAL**

a. United States Patent Number 7,879,842	b. Issue Date of Patent 02/01/2011	c. Expiration Date of Patent 02/22/2026
d. Name of Patent Owner Les Laboratoires Servier	Address (of Patent Owner) 35 rue de Verdun	
	City/State Suresnes, Cedex	
	ZIP Code France	FAX Number (if available) 0033 1 55 72 57 72
	Telephone Number 0033 1 55 72 60 00	E-Mail Address (if available) mail.patent12-def@fr.netgrs.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Stuart Watt Amgen Inc.	Address (of agent or representative named in f.a.) One Amgen Center Drive	
	City/State Thousand Oaks, CA	
	ZIP Code 91320-1799	FAX Number (if available) (805) 499-8011
	Telephone Number (805) 447-2154	E-Mail Address (if available) swatt@amgen.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes <input type="checkbox"/> No	

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?
4,6	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) TRADENAME (ivabradine) is indicated to reduce the risk of cardiovascular mortality or hospitalizations for worsening heart failure in patients with chronic heart failure NYHA Class II to IV with systolic dysfunction and in sinus rhythm with heart rate $\geq$ 70 beats per minute (bpm), in combination with standard therapy including maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated or not tolerated.
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**5. No Relevant Patents**

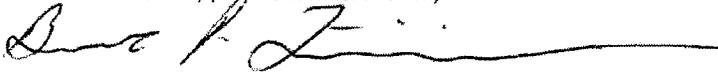
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably 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

04/30/2014

**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

Bernard P. Friedrichsen, Senior Counsel

Address

One Amgen Center Drive

City/State

Thousand Oaks, CA

ZIP Code

91320-1799

Telephone Number

(805) 447-0628

FAX Number (if available)

(805) 499-8011

E-Mail Address (if available)

bernardf@amgen.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**\*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.\***

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
Paperwork Reduction Act (PRA) Staff  
[PRStaff@fda.hhs.gov](mailto:PRStaff@fda.hhs.gov)

*"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 number."*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

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

**First Section**

Complete all items in this section.

**I. General Section**

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

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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

**2. Drug Substance (Active Ingredient)**

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

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

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

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

**4. Method of Use**

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

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

# Attached Sheet for Form 3542a US Patent No. 7,879,842

An application for a United States Adopted Name (USAN) was filed in December of 2013, to obtain approval of the generic names ivabradine and ivabradine hydrochloride. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine dated April 29, 2014, has now been received. A STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL for ivabradine hydrochloride dated April 30, 2014, has also now been received.

Ivabradine has been approved as an International Nonproprietary Name (INN) by the World Health Organization (WHO). The INN number is 7523.

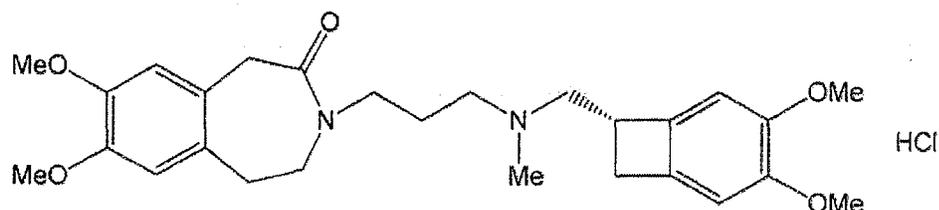
The Chemical Abstract Service (CAS) Registry Number for the hydrochloride salt form is 148849-67-6. The CAS Registry Number for the base form is 155974-00-8. The CA Index Name for the hydrochloride salt is provided below

2H-3-Benzazepin-2-one, 3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-, hydrochloride (1:1).

A synonym for this name is provided below.

3-(3-[[[(7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamino]propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride

The structure of the compound is shown below.



## EXCLUSIVITY SUMMARY

NDA # 206143

SUPPL # n/a

HFD # 110

Trade Name: Corlanor

Generic Name: Ivabradine

Applicant Name: Amgen, Inc.

Approval Date, If Known: Exact Date Not Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

n/a

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

n/a

d) Did the applicant request exclusivity?

YES  NO

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

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?

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. (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: Alexis Childers  
Title: Senior Regulatory Health Project Manager  
Date: March 10, 2015

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD  
Title: Director, Division of Cardiovascular and Renal Products

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALEXIS T CHILDERS  
03/10/2015

NORMAN L STOCKBRIDGE  
03/10/2015

**Debarment Certification**

Amgen 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.

*Mary Ellen Cosenza*

Mary Ellen Cosenza  
Executive Director, US Regulatory Affairs

*Jan 13, 2014*

Date

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**AMGEN**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206143 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Corlanor Established/Proper Name: Ivabradine Dosage Form: 5 mg & 7.5 mg Tablets		Applicant: Amgen Inc Agent for Applicant (if applicable): n/a
RPM: Alexis Childers		Division: Cardiovascular and Renal Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p style="margin: 0;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:         </p> <p style="margin: 0;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>May 27, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 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).

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

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

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Fast Track            | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review        | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: April 15, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	9/23/14 9/22/14
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 8/27/14 DMEPA: <input type="checkbox"/> None 11/26/14, 3/2/15 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input type="checkbox"/> None 3/9/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None 3/9/15
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	8/18/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>9/3/14</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ 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.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	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 <ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 1/23/14 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A 10/6/14 <input type="checkbox"/> N/A 12/10/14 Topline: 1/22/14, CMC Pre-NDA 12/23/13
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/15/15
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/4/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/8/14
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	12/17/14, 12/18/14, 12/19/14 8/5/14, 12/4/14 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical review dated 12/4/14 page 27, and 12/19/14 from CDTL
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None 3/3/15
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 12/15/14
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review co-signed reviewers review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/5/14, 11/17/14
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review co-signed reviewers review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	8/13/14, 11/26/14, 4/11/15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	4/8/15
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review co-signed reviewers review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/7/14, 11/18/12, 11/19/14, 11/25/14, 11/28/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	10/5/14
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 8/28/14 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	Not required

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review co-signed reviewers review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None biopharm 11/21/14, CMC 12/2/14
<b>❖ Microbiology Reviews</b> <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	6/6/14
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	12/2/14
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
<b>❖ Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: <input checked="" type="checkbox"/> Acceptable see chemistry note <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

<b>Day of Approval Activities</b>	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> ) <b>N/A</b>
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done <b>N/A</b>
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> ) <b>N/A</b>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALEXIS T CHILDERS  
04/15/2015

MEMORANDUM

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

DATE: March 30, 2015

TO: Christine Kubik, Senior Manager, Regulatory Affairs, Amgen

FROM: Alexis Childers, Sr. RPM, Division of Cardiovascular and Renal Products

SUBJECT: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website

**APPLICATION/DRUG: NDA 206143/ivabradine**

Dear Ms. Kubik,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, ivabradine, currently under review in the Division. If the application is approved, this information will be posted publically at the FDA drug snapshot website:

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>

We are asking for this information and making it public to allow for greater transparency into participation in clinical trials for newly-approved drugs and biologics.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at [Drugs@FDA](mailto:Drugs@FDA)

Information will be published approximately 30 days after drug approval.

Therefore, we are requesting that you provide your data and complete the attached tables as well as provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data, if these are not already in the NDA 206143 submission.

We are requesting you submit this information no later than Friday April 3, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,  
Alexis Childers, RAC  
Senior Regulatory Project Manager  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I

Attachments: Proposed Shell Tables for Completion

**Table 6.1.1 Listing of Clinical Trials for the Efficacy Analysis** (SHIFT Only)

<b>Study ID</b>	<b>No. of patients enrolled in Treatment</b>	<b>No. of patients enrolled in Control</b>

**Table 6.1.2-a. Baseline Demographics, Pivotal Efficacy Trial (SHIFT Randomized Set N=6505)**

Demographic Parameters	Treatment Group(s)		Total (N=)
	Treatment Group (N=) n (% , )* [%PY]	Control (N=) n (%)* [%PY]	
<b>Sex</b>			
Male			
Female			
<b>Age</b>			
Mean years (SD)			
Median (years)			
Min, Max (years)			
<b>Age Group</b>			
<17 years			
>=17 - <65 years			
>=65 years			
>=75 years			
<b>Race</b>			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
<b>Ethnicity</b>			
Hispanic or Latino			
Not Hispanic or Latino			
<b>Region (optional)</b>			
United States			
Rest of the World			
Canada			
South America			
Europe			
Asia			
Africa			
Source: * Percentages are calculated based on the total number of subjects in the respective arm. For example, percentage of males in Treatment Group 1 = 25/50			

Table 6.1.7 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trial (SHIFT Randomized Set N=6505)

Subgroup	Treatment (N=XX)		Control (N=XX)		Hazard Ratio**	95% CI	
	x (%)* [%PY]	Total, n	x (%)* [%PY]	Total, n		LL	UL
<b>Overall Response/All patients</b>							
<b>Sex</b>							
Male							
Female							
<b>Age Group</b>							
<17 years							
>=17 - <65 years							
>=65 years							
>=75 years							
<b>Race</b>							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
<b>Ethnicity</b>							
Hispanic or Latino							
Not Hispanic or Latino							
<b>Region (optional)</b>							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source:

\*Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentage of male responders in treatment group = 20/30

\*\* Designated per review, other options are Risk Difference, Relative Risk, etc

**Table 7.1.1 Safety Population, Size and Denominators**

<b>Safety Database</b>			
<b>Individuals exposed to the study drug in this development program for the indication under review</b>			
<b>N = (N is the sum of all available numbers from the rows below)</b>			
<b>Clinical Trial Groups</b>	<b>New Drug (n= )</b>	<b>Active Control (n= )</b>	<b>Placebo (n= )</b>
Normal Volunteers			
Controlled trials conducted for this indication			
All other than controlled trials conducted for this indication			
Controlled trials conducted for other indications			

**Table 7.2.1-a. Baseline Demographics, SHIFT Safety Population**

Demographic Parameters	Treatment Group(s)		Total (N=6538)
	Ivabradine (N=3260) n (%, )* [%PY]	Placebo (N=3278) n (%, )* [%PY]	
<b>Sex</b>			
Male			
Female			
<b>Age</b>			
Mean years (SD)			
Median (years)			
Min, Max (years)			
<b>Age Group</b>			
<17 years			
>=17 - <65 years			
>=65 years			
>=75 years			
<b>Race</b>			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
<b>Ethnicity</b>			
Hispanic or Latino			
Not Hispanic or Latino			
<b>Region (optional)</b>			
United States			
Rest of the World			
Canada			
South America			
Europe			
Asia			
Africa			
Source: * Percentages are calculated based on the total number of subjects in the respective arm. For example, percentage of males in Treatment Group 1 = 25/50			

Table 7.5.3-a. Subgroup Analysis of AEs, SHIFT Safety Population

Subgroup	Ivabradine (N=3260)		Placebo (N=3278)			Relative Risk***	95% CI	
	x (%)* [%PY]	Total, n	x (%)**	[%PY]	Total, n		LL	UL
<b>Any TEAEs*</b>								
<b>Sex</b>								
Male								
Female								
<b>Age Group</b>								
<17 years								
>=17 - <65 years								
>=65 years								
>=75 years								
<b>Race</b>								
White								
Black or African American								
Asian								
American Indian or Alaska Native								
Native Hawaiian or Other Pacific Islander								
Other								
<b>Ethnicity</b>								
Hispanic or Latino								
Not Hispanic or Latino								
<b>Region (optional)</b>								
United States								
Rest of the World								
Canada								
South America								
Europe								
Asia								
Africa								

Source:

\*Designate per review, other options are SAEs or AEs of special interest (for instance, an HLT, SOC, or user-designated group of PTs)

\*\* Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentage of males with TEAEs in treatment group = 25/30

\*\*\*Designated per review, other options are Risk Difference, Hazard Ratios, etc

Table 7.5.3-a. Subgroup Analysis of SAEs, SHIFT Safety Population

Subgroup	Ivabradine (N=3260)		Placebo (N=3278)			Relative Risk***	95% CI	
	x (%)* [%PY]	Total, n	x (%)**	[%PY]	Total, n		LL	UL
<b>Any TEAEs*</b>								
<b>Sex</b>								
Male								
Female								
<b>Age Group</b>								
<17 years								
>=17 - <65 years								
>=65 years								
>=75 years								
<b>Race</b>								
White								
Black or African American								
Asian								
American Indian or Alaska Native								
Native Hawaiian or Other Pacific Islander								
Other								
<b>Ethnicity</b>								
Hispanic or Latino								
Not Hispanic or Latino								
<b>Region (optional)</b>								
United States								
Rest of the World								
Canada								
South America								
Europe								
Asia								
Africa								

Source:

\*Designate per review, other options are SAEs or AEs of special interest (for instance, an HLT, SOC, or user-designated group of PTs)

\*\* Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentage of males with TEAEs in treatment group = 25/30

\*\*\*Designated per review, other options are Risk Difference, Hazard Ratios, etc

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/s/  
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ALEXIS T CHILDERS  
03/30/2015



NDA 206143

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Amgen Inc.  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ivabradine, 5 and 7.5 mg tablets.

On September 8, October 27 and 30, 2014, we received the SIGNIFY study results and data and have classified these submissions as a, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 28, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 21, 2015.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

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

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/s/  
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NORMAN L STOCKBRIDGE  
12/15/2014



NDA 206143

**INFORMATION REQUEST**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ivabradine, 5 and 7.5 mg tablets.

We have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Provide a summary of the world-wide experience with ivabradine exposure in pregnant women with regard to pregnancy outcomes (i.e., abortion, congenital abnormalities, fetal toxicity, and teratogenicity). Summary should include, but not necessarily be limited to, data from relevant pregnancy exposure registries, observational studies, post-marketing adverse event reports, and clinical trials. If your PSUR-11 (120 day safety update) for NDA 206143 contains all ivabradine pregnancy exposures from all of these sources, then the information in that document will suffice.

Consider submitting revised labeling in accordance with the recently published Pregnancy and Lactation Labeling Rule (“Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling” found at <https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for>)

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, Pharm.D.  
Deputy Director for Safety  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MARY R SOUTHWORTH  
12/10/2014



NDA 206143

**DEFICIENCIES PRECLUDE DISCUSSION**

Amgen Inc.  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your June 27, 2014 New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for for Ivabradine, 5 and 7.5 mg tablets.

We also refer to our August 25, 2014, letter in which we notified you of our target date of December 9, 2014 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have determined that open issues to be discussed at the January 14, 2015 Cardiovascular and Renal Products Advisory Committee meeting preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, please call Alexis Childers, Regulatory Project Manager, at (301) 301-796-0442.

Sincerely,

*{See appended electronic signature page}*

Thomas Marciniak, MD  
Cross-Discipline Team Leader  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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THOMAS A MARCINIAK  
12/09/2014



NDA 206143

**MID-CYCLE COMMUNICATION**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) dated June 27, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ivabradine, 5 and 7.5 mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on October 6, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

Thomas Marciniak, M.D.  
CDTL  
Division of Cardiovascular and 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

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** October 6, 2014, 1:00 pm  
**Application Number:** 206143  
**Product Name:** Ivabradine  
**Indication:** **Treatment of heart failure**  
**Applicant Name:** Amgen Inc.

**Meeting Chair:** Thomas Marciniak, M.D.  
**Meeting Recorder:** Alexis Childers, RAC

**FDA ATTENDEES**

*\*Division of Cardiovascular and Renal Products*

Tom Marciniak, M.D. Clinical Team Leader (CDTL)  
Preston Dunnmon, M.D. Clinical Reviewer  
Nhi Beasley, Pharm.D. Clinical Reviewer  
Jean Wu, Ph.D. Pharmtox Reviewer  
Alexis Childers, RAC Sr. Regulatory Health Project Manager

*\*Office of Clinical Pharmacology*

Martina Sahre, Ph.D. Clinical Pharmacology Reviewer  
Rajanikanth Madabushi, Ph.D. Clinical Pharmacology Team Leader

*\*Office of Biostatistics, Division of Biometrics I*

Steve Bai, Ph.D. Statistician

*\*Office of New Drug Evaluation*

Wendy Wilson, Ph.D. Chemistry reviewer  
Sandra Suarez, Ph.D. Biopharmaceutics reviewer

*\*Office of Surveillance and Epidemiology*

Susan Lu, RPH, Safety Evaluator Team Leader  
Oanh Dang, Pharm D, BCPS Safety Evaluator  
Margie Goulding, Ph.D. Epidemiology Team Leader  
Kim Lehrfeld, PharmD Team Leader, DRISK  
Danny Gonzalez, PharmD, M.S. Risk Management Analyst, DRISK

**APPLICANT ATTENDEES**

Mariano Janiszewski, Ph.D. Global Safety Sr. Medical Scientist  
Christophe Depre, M.D. Clinical Research Medical Director  
Lisa DiMolfetto, Ph.D. Regulatory Affairs Director  
Robert Scott, M.D. VP Global Development  
Laurence Gamelin, MD, MS, PhD Global Safety Medical Director  
John Wisler, Ph.D., DABT Scientific Director (Nonclinical)  
Rameshraj Palaparthi, Ph.D. Principal Scientist

Jae Kim, MD, FACC	Clinical Research Medical Director
Chao-Yin Chen, Ph.D.	Biostatistics Sr. Manager
Dominique Bertin-Millet, M.D.	Executive Medical Director Global Safety
Juan Maya	Executive Medical Director Global Development
Nina Cauchon, Ph.D., RAC	Regulatory Affairs Sr. Manager (CMC)
Geza Ekecs	Regulatory Affairs Sr. Manager (CMC)
Arline Nakanishi , M.S.	Executive Director Biostatistics
Graham Jang, PhD, MBA	Medical Sciences Director
Shirley Douglass, CW	Product Project Manager
Maryam Sadat	Compliance Sr. Manager
Christine Kubik	Regulatory Affairs Sr. Manager
Jennifer Vande Weghe	Regulatory Writing Sr. Manager
Chanda Walton	Regulatory Affairs Director

## 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

### **Clinical:**

Dr. Marciniak stated that while the pivotal trial SHIFT, appeared to be a favorable study with a lean on mortality there are several questions. He stated that the reviews are ongoing and while we have definitely not concluded that the application is not approvable, the following issues need to be addressed to insure approvability and enable adequate labeling:

- a. Inconsistencies among the three trials. While SHIFT as one study appears to show a benefit of ivabradine, the three CV outcome trials SHIFT, BEAUTIFUL, and SIGNIFY appear to be highly inconsistent. In SHIFT the major benefit of ivabradine in the study as a whole was a reduction in heart failure (HF) hospitalizations while results for myocardial infarctions (MIs) were neutral. In BEAUTIFUL HF hospitalization results were neutral while there appeared to be an ivabradine benefit for MI. The latter result inspired SIGNIFY but SIGNIFY failed to confirm a benefit and in fact suggests a detrimental effect in patients with symptomatic angina. Ideally we need to understand the reasons for these different trial results to understand for which patients' ivabradine is useful and to determine if there is a heart failure benefit.

- b. SIGNIFY results and relevance to the HF indication. SIGNIFY was at best neutral--leaning negatively--for CV and all-cause mortality in the study as a whole and worse than placebo for the primary endpoint in the subgroup with symptomatic angina and leaning worse in that subgroup for CV mortality. While SIGNIFY patients did not have heart failure, 69% of SHIFT patients had ischemic heart disease, the primary entry criterion for SIGNIFY, and ischemic heart disease is the predominant etiology for U.S. heart failure patients. We judge SIGNIFY results to be relevant to the HF indication. We need to understand how they apply—or how they are not applicable—to HF patients with an ischemic etiology. We hypothesize that one difference may be the differing rates of use of loop diuretics in SHIFT and SIGNIFY (and in BEAUTIFUL) with the observed interaction between ivabradine and loop diuretic use for CV mortality in SHIFT. We need to understand if there is a CV mortality problem.
- c. The SHIFT data suggest a possible interaction with statin use. Dr. Marciniak stated that the interaction is only apparent in SHIFT. He suggested that perhaps the interaction seen in SHIFT was because some patients were non-ischemic where as in BEAUTIFUL all patients were ischemic.

Dr. Dunnmon stated that the different outcomes in SHIFT and SIGNIFY are concerning. He stated his concerns as follows:

- d. Drug- induced bradycardia. You have suggested that the nominally significant increase in the composite end point (CEP) of CV death and non-fatal MI in the 12,049 patient subgroup experiencing angina from SIGNIFY (with a negative lean on both components of the composite) may have been due to the higher dose of ivabradine used in SIGNIFY, which resulted in more bradycardia, which caused decreased diastolic pressures, decreased coronary perfusion, and increased CV death and MI in these patients. While all patients in SIGNIFY had coronary artery disease (CAD), this was likewise the case for the vast majority of patients in SHIFT, 68 percent of whom had an ischemic heart disease as the basis for their HF<sub>r</sub>EF. If anything, these SHIFT patients would seem to be at a substantially greater risk from the mechanism for harm that you have proposed in SIGNIFY because:
  - i. SHIFT patients were arguably much sicker, with a mean ejection fraction of 29% versus a mean ejection fraction of 56% in SIGNIFY
  - ii. In that cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV), and given that SV in SHIFT patients was a low number, these patients by necessity will be more rate dependent for cardiac output. Thus, a disproportionate decrease in HR in these patients would be expected to have even more profound deleterious consequences in SHIFT patients than in SIGNIFY patients if your proposed mechanism of harm is correct (diastolic hypoperfusion of obstructed coronary arteries leading to ischemia, MI, and potentially ischemia/bradycardia mediated life threatening ventricular arrhythmias).

Accordingly, it must be pointed out that the inclusion criteria for baseline heart rate in SHIFT and in SIGNIFY were the same (70 bpm), and that the target post-baseline heart rate that was sought by dose titration was actually higher in SIGNIFY (55-60 bpm) than it was in SHIFT (50-60 bpm, which is likewise the target HR range for therapy based on your proposed labeling). You might argue that while the target heart rate was lower in SHIFT than in SIGNIFY, the actual achieved mean heart rate achieved in SHIFT was higher than in SIGNIFY (65 bpm versus 60 bpm, respectively), and that the dose of ivabradine administered in SHIFT was commensurately lower than in SIGNIFY (6.4±1.4 mg BID versus 8.2±1.7 mg BID, respectively). However, this argument suffers from the following limitations:

- i. Overall, the SHIFT investigators did not dose to the protocol specified heart rate range that is now being used to direct dosing in your proposed label.
  - ii. If the difference between a mean heart rate of 60 bpm in SIGNIFY and 65 bpm in SHIFT is the difference between a trial that causes CV harm in CAD patients and one that does not, then the therapeutic index of ivabradine is indeed exquisitely narrow.
  - iii. You are recommending a target heart range in the proposed SHIFT label that the SHIFT trial overall did not achieve, a rate range of 50-60, understanding that the mean rate achieved in SIGNIFY, a trial which showed harm in its large angina subset, was 61 bpm. Therefore, the possibility that your proposed mechanism for harm in SIGNIFY is correct (i.e. drug-induced bradycardia leading to coronary hypoperfusion and ischemia) creates an inherent conflict with respect to how to appropriately dose/label ivabradine in CHF patients based on post-baseline heart rates measured in the clinic.
- e. Drug-induced atrial fibrillation. Dr. Dunnmon noted that the development of new onset atrial fibrillation (afib) in CHF patients has been shown to be associated with increased mortality (Wang et al. Circulation. 2003; 107:2920-2925). Ivabradine appears to be causing an excess of afib. The absolute incremental afib risk in SHIFT was approximately 1.7% (relative increase 25%). Consequently, there were more patients with afib adverse events in SHIFT's ivabradine treatment group compared to placebo (306 versus 251, respectively). All six cases of TEAE sick sinus syndrome during the SHIFT treatment period occurred in the ivabradine treatment group. In SHIFT, afib was serious in nearly half of subjects with an event and had a fatal outcome in 1 subject (ivabradine group). This has been a reproducible finding: in SIGNIFY, the absolute increase in afib in the group of patients having angina was 1.4% (relative increase 44%). The Division believes that the occurrence of ivabradine-induced afib is at least as frequent as you have observed in your clinical trials, but is likely higher, given that none of these trials were designed for the ascertainment of paroxysmal afib.

Dr. Beasley noted that the rate of afib between the two treatments starts to separate around 6 months in SHIFT. That observation raised the question whether the drug is

structurally affecting the heart. The applicant could confirm this with the proper imaging studies.

f. Effects on the conduction system, other than at the SA node. (b) (4)

In SHIFT, 5 of 7 patients experiencing severe TEAEs of third degree AV block were in the ivabradine treatment group, and 6 of the 8 patients experiencing severe TEAEs of complete AV block were in the ivabradine treatment group. The potential for the concurrent occurrence of afb and high degree AVB may explain the above mentioned imbalance in the occurrence of sick sinus syndrome TEAEs during the SHIFT treatment period (6 versus 0).

g. Trials conducted outside of the US. The use of devices with proven efficacy for the reduction of CV death and/or hospitalization for worsening heart failure as background therapy in SHIFT did not and does not reflect contemporary US practice. For example, for patients with a LVEFs < 35% and LBBB (QRS  $\geq$  150 msec, NYHA class  $\geq$  II), CRT therapy carries a class-I recommendation in the 2012 ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, and has been shown to reduce hospitalizations and mortality. It is unclear that ivabradine would confer any additional mortality and/or hospitalization benefit in the CRT-treated population. For those patients without LBBB, ICD therapy would be indicated in the US for most all (class I recommendation, LVEF  $\leq$  35% and NYHA II-III, or IHD with LVEF < 30% and NYHA I). Assuming that patients with ICDs but without CRT might benefit from decreased hospitalizations for worsening heart failure (WHF) with ivabradine (as additional mortality benefit from ivabradine on top of an ICD therapy has not been demonstrated), the character and ascertainment of these WHF hospitalizations at sites outside the US as compared to US practice becomes important to assess. We are particularly interested in the possibility that bias may have been imparted to the decision to admit based on knowledge of the patients' heart rate responses to study drug (i.e., the potential that functional unblinding of the trial may have influenced the WHF hospitalization component of the composite primary efficacy endpoint that drove the overall trial results).

### Clinical Pharmacology

Drug-drug interaction in labeling: Dr. Sahre stated that the labeling with regard to drug-drug interactions and intrinsic factors will need some revision. The statement (b) (4) should be turned into an actionable item as much as possible. For CYP3A4 inducers, the statement reads (b) (4) This language needs to be made more precise and actionable. The Division will provide some language during label negotiations.

### 3.0 INFORMATION REQUESTS:

- a. The Division requested datasets and CRFs from SIGNIFY. Amgen will provide during the week of November 3, 2014.

- b. The Division would like the sponsor to provide their rationale for the difference in heart rate between SHIFT and SIGNIFY and how to label such a fine line with dose, heart rate etc.
- c. The Chemistry reviewers received the sponsor's response and are currently reviewing.

**4.0 MAJOR SAFETY CONCERNS:** Effects of excessive bradycardia, increased atrial fibrillation rates, and CV mortality in SIGNIFY. See Significant Review Issues.

**5.0 RISK MANAGEMENT UPDATE:** Currently the Agency believes a REMS is not necessary to ensuring the benefits of Ivabradine outweigh the risks.

**6.0 ADVISORY COMMITTEE MEETING PLANS:** The AC Meeting is scheduled for January 14, 2015.

**7.0 PROPOSED DATE FOR LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES:** The LCM is scheduled for December 10, 2014 and. Label negotiations should begin December 9, 2014.

**8.0 ADDITIONAL DISCUSSION**

Amgen asked if it would be helpful to provide the following additional analysis and information:

- a. Provide further DDI information in terms of SIGNIFY dataset to provide further context.
- b. Prepare a White paper discussing electrophysiology mechanisms in the context of afib and tachycardia devices.
- c. Provide an analysis by baseline angina subgroup.

The Division stated they would be interested in reviewing all of the above mentioned items. The Division requested that datasets and SAS programs be included with any additional reports. They also asked for an informal teleconference to have further discussion regarding all of the topics mentioned. The Division stated that the sponsor should look at subgroups for which there may be a heart failure, mortality or stroke benefit.

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/s/  
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THOMAS A MARCINIAK  
10/21/2014



NDA 206143

**METHODS VALIDATION  
MATERIALS RECEIVED**

Amgen  
Attention: Christine Kubik  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
Kubik, Christine <ckubik@amgen.com>

Dear Christine:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ivabradine 5 mg and 7.5 mg film coated tablet and to our August 18, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on September 25, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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MICHAEL L TREHY  
10/20/2014

**From:** [Knight, Yvonne](#)  
**To:** [ckubik@amgen.com](mailto:ckubik@amgen.com)  
**Cc:** [Knight, Yvonne](#)  
**Subject:** Information Request for NDA 206143 (Prompt Response)  
**Date:** Thursday, September 25, 2014 3:41:06 PM  
**Importance:** High

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Good afternoon Ms. Kubik,

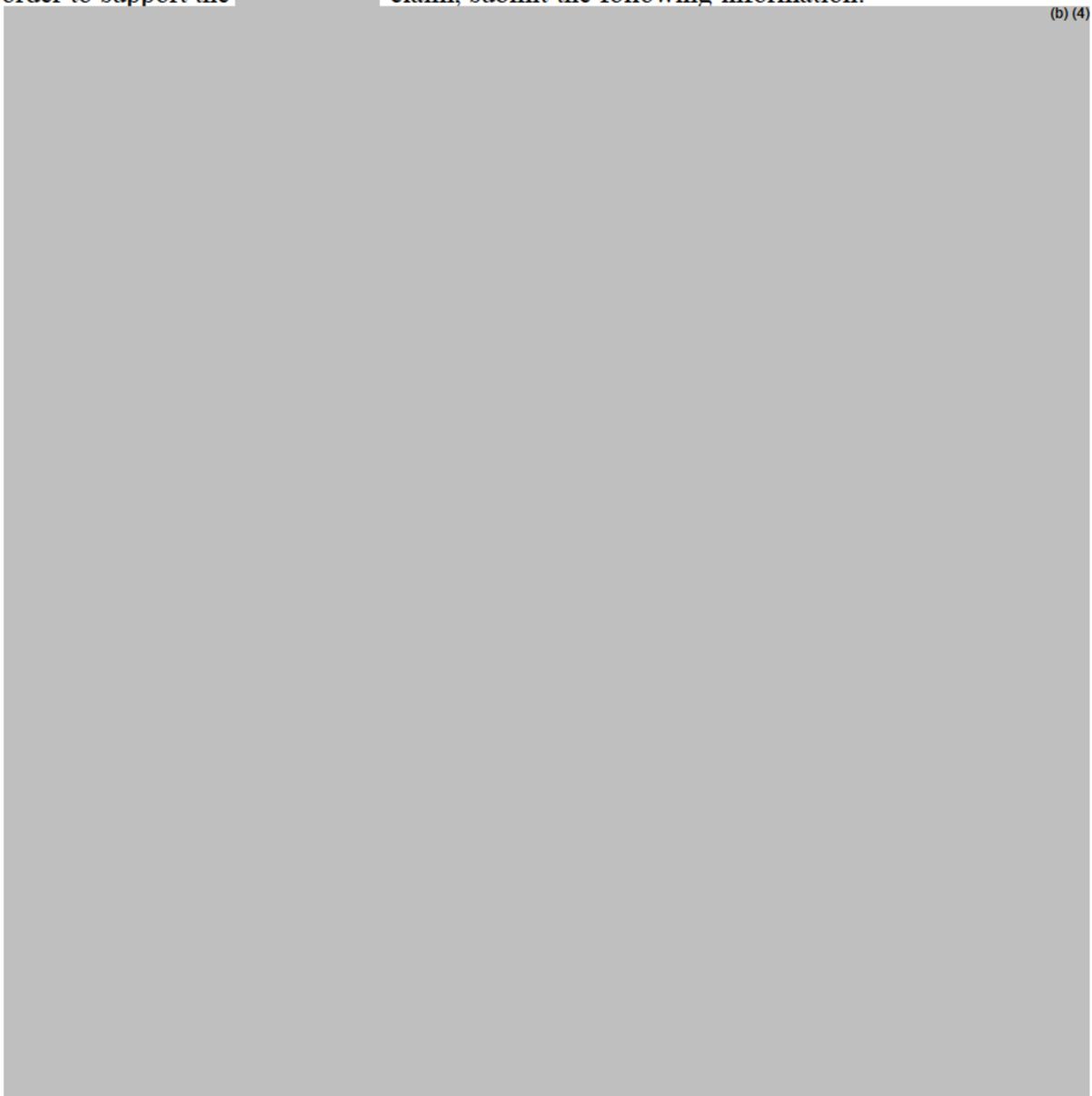
We have an information request concerning Amgen's New Drug Application (NDA) for NDA 206143. We are reviewing the **Quality** section of your submission and have the following comments and information requests. We request a prompt written response by **Friday COB October 3, 2014**, in order to continue our evaluation of your NDA.

1. Clarify if the proven acceptable ranges (PARs) included in Section 3.2.S.2.2 of the submission constitute a proposal for a drug substance manufacturing design space and regulatory flexibility. The footnote in Section 3.2.S.2.2.1.3 indicates that changes can be made to the GMP intermediate loads based on attributes associated with the proposed PARs.
2. Comment on the control strategy for the (b) (4) used during the ivabradine (b) (4) process. The information in Sections 3.2.S.2.2 and 3.2.S.3.2 do not include controls for (b) (4)
3. Include a limit for individual, unspecified impurities in the (b) (4) specification. The proposed specification only controls total impurities content. A control for individual, unspecified impurities provides additional assurance of purity and quality and will allow for trend analysis of impurities that may require additional controls as specified impurities.
4. Comment on the test methods used to confirm the identity of the (b) (4) reagents. The submission did not list tests or criteria for identity for either reagent. The submission indicates that identity tests are performed on all raw materials. If identity tests are not performed for these materials, provide justification for not including identification as part of the specification.
5. Comment on how the control strategy for impurities – including the genotoxic impurities – will be evaluated in light of any changes to the drug substance manufacturing process. The proposed ivabradine control strategy relies on the manufacturing process and control of materials to reduce the content of genotoxic impurities in the final drug substance.
6. As the USP/NF compendia is the official compendia in the United States, provide justification for the use of European Pharmacopeia standards for the potentiometric titration, (b) (4) HPLC, FT-IR, and optical rotation analytical procedures. Provide copies of the standards referenced in the European Pharmacopeia. Provide a statement acknowledging that the corresponding USP/NF analytical procedure is the official regulatory analytical procedure.

7. Identify the proposed regulatory and the proposed alternate analytical procedure for (b) (4) determination. Identify the criteria that trigger use of the alternate method instead of the regulatory method. The submission lists determination of (b) (4) by either (b) (4) without specifying the regulatory method (Section 3.2.S.4.2) but only lists coulometry in the proposed regulatory specification (Section 3.2.S.4.1).

8. Provide data demonstrating the accuracy of the assay and (b) (4) content (b) (4) analytical procedures or provide justification for not including accuracy as a method validation criterion. Accuracy is a typical characteristic evaluated for analytical procedures used to control content or potency (reference the ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology Guidance). Because the titration method was not demonstrated to be specific, accuracy of the methods cannot be inferred.

9. In order to support the (b) (4) claim, submit the following information:



10. To support the use of disintegration in lieu of dissolution testing provide:
  - a. Data showing a correlation between disintegration and dissolution testing.
  - b. Disintegration and dissolution profiles as a function of changes in tablet hardness.
  - c. To ensure that disintegration testing is able to pick up possible changes in the dissolution rate of your product that may occur during stability, provide disintegration and multipoint dissolution profile data for the registration batches throughout the stability time-period supporting the shelf-life of your product.
11. List all the formulation/manufacturing changes/differences between the commercial formulation and the formulation tested in pivotal phase III trials.

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

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

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/s/  
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YVONNE L KNIGHT  
09/25/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206143

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Amgen Inc.  
9201 Corporate Boulevard  
Suite 400  
Rockville, MD 20850

ATTENTION: Christine Kubik  
Senior Manager, Regulatory Affairs

Dear Ms Kubik:

Please refer to your New Drug Application (NDA) submitted and received June 27, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ivabradine Tablets, 5 mg and 7.5 mg.

We also refer to your correspondence, submitted and received June 27, 2014, requesting review of your proposed proprietary name, Corlanor.

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

If any of the proposed product characteristics as stated in your June 27, 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 Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Alexis Childers, Regulatory Project Manager in the Office of New Drugs, at (301)796-0442.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
09/23/2014



NDA 206143

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) dated June 27, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ivabradine, 5 and 7.5 mg tablets.

We also refer to your amendments dated July 11, 18, 22, 25, 30, and August 1, 6, 8, 11(2), 13, 14 and 18 (2) 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. 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 February 27, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 9, 2014. In addition, the planned date for our internal mid-cycle review meeting is September 25, 2014. We are tentatively 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:

### **CMC**

1. Include a method validation package in 3.2.R that is consistent with the *FDA 1987 guideline for submitting samples and analytical data for method validation*. Include links for the following information:
  - Composition of the drug product,
  - Listing of the proposed regulatory specifications,
  - Information supporting the integrity of the reference standard,
  - Detailed description of each method of analysis, including information supporting the suitability of the methodology for the drug substance, and
  - Detailed description of each method of analysis, including information supporting the suitability of the methodology for the drug product.
  - A tabular listing of all samples to be submitted
2. Provide updated 9 month stability data for the drug product packaged in bottles as soon as they become available.

### **Clinical Pharmacology**

1. Your Clinical Pharmacology Summary states that (b) (4)  
  
However, neither the Summary, nor the label refers to a potential interaction. Have any studies been done to substantiate this potential drug-drug interaction? If none have been done, how do you plan to address the issue?

### **Clinical**

1. **Financial disclosures**. SHIFT was conducted exclusively outside of the United States, not under an IND, and so US financial disclosure information was not initially requested. Approximately two years after SHIFT was completed, in 2012, an attempt was begun to collect this information.. The response rate of the investigators over the 628 SHIFT sites was low.
2. **Confirmation of data integrity**. FDA is unable to audit data from the two highest enrolling countries (Russia and Ukraine).
3. **Relevance to US patients and US medical practice**. We question the relevance of the efficacy data to treatment of HF<sub>r</sub>EF in the US, because SHIFT was conducted in a heart failure population with a mean LVEF of 29% in whom device therapy (specifically ICD and CRT) was discouraged. The two components of the primary composite endpoint in the single pivotal trial, SHIFT, were CV mortality and hospitalization for worsening heart failure in subjects with moderate to severe symptoms of chronic heart failure. In this group of HF<sub>r</sub>EF patients, implantable cardioverter/defibrillator devices (ICDs) have been shown to decrease CV mortality, and in those with a widened QRS, cardiac resynchronization therapy (CRT) has been shown to reduce CHF hospitalization and CV mortality. It is unclear that ivabradine would have demonstrated a clinical benefit above and beyond what is conferred by device therapy as incorporated into contemporary US medical practice. Analysis of the trial outcomes in patients who would not have qualified for device therapy according to ACC-AHA guidelines will be of interest.

4. Atrial proarrhythmia. Ivabradine was associated with the development of atrial fibrillation and/or atrial flutter, not only in SHIFT, but also in the small clinical pharmacology studies (b) (4). Study CL2-045 suggests that ivabradine may also prolong PR and AH intervals. These two findings are of particular concern given that in SHIFT, ivabradine therapy was associated with increased occurrences of the following treatment-emergent adverse events (TEAEs) relative to placebo (from the clinical overview, rates, where given, are expressed as ivabradine, placebo):

- Bradycardia (4.6% [2.7%PY], 0.9% [0.5%PY])
- Heart rate decreased (5.6% [3.4%PY], 1.4% [0.8%PY])
- Serious bradycardia events were reported in 18 ivabradine-treated subjects, of whom 12 were hospitalized (as opposed to 2 placebo-treated subjects, randomization 1:1). These episodes were accompanied by symptoms ranging from weakness and dizziness to dyspnea, chest pain, hypotension, presyncope, and syncope. Four out of 18 reported cases in the ivabradine group required medical resuscitation (atropine, isoprenaline, dopamine, IV fluids). Half of the serious bradycardia events resulted in withdrawal from SHIFT.
- Serious third degree AV block (0.3% [0.2%PY], 0.1% [ $<0.1\%$  PY])\*
- Atrial fibrillation (8.3% [4.9%PY], 6.7% [4.0%PY]). Atrial fibrillation was serious in nearly half of subjects with an event and had a fatal outcome in 1 subject (ivabradine group).
- Serious atrial flutter (0.68% [0.41%PY], 0.58% [0.35%PY])
- Six cases of sick sinus syndrome were reported in ivabradine group versus none in placebo group during the treatment period.
- Third degree and sick sinus syndrome (serious and nonserious occurrences taken together) led to discontinuation of study drug more frequently in the ivabradine group than in the placebo group (0.2% [0.1%PY] vs 0.1% [ $<0.1\%$  PY] and 0.2% [0.1%PY] vs 0% [0%PY], respectively)

The above noted findings have led you to the conclusion that ivabradine therapy should not be used in patients with atrial fibrillation. We agree with that assessment. However, the occurrence of atrial fibrillation in the studied population was common – atrial fibrillation was the preferred term which most frequently led to study drug discontinuation in both arms of SHIFT, though its frequency appears to be exacerbated by the use of ivabradine. We are concerned at this point that the occurrence of important bradycardia events, some in the setting of atrial fibrillation which may be associated with a profoundly slow ventricular response rate, may result in a higher incidence of poor CV outcomes if these indeed occur outside of the closely monitored setting of a controlled clinical trial.

5. Ventricular Proarrhythmia. From SHIFT, you conclude that ivabradine prolongs the QT interval through its effect on heart rate, but does not prolong the QTc. However, serious treatment-emergent ventricular fibrillation was more common in the ivabradine treatment group (0.62% [0.37%PY], 0.34% [0.20%PY]), and more of these events resulted in fatal outcomes for ivabradine-treated patients (11 versus 3). In addition, two cases of treatment-emergent Torsade de Pointes occurred in ivabradine-treated patients, one of which resulted in syncope. From this information, (b) (4)

However, it is unclear to what degree these

ventricular arrhythmias were bradycardia mediated, the degree to which CRT therapy would have prevented these events had it been allowed in the trial, and the degree to which these fatalities would have been averted had ICD therapy had been incorporated into SHIFT per contemporary US practice standards.

6. Ivabradine-induced elevations of blood pressure. In shift, a greater mean (SD) increase in sitting systolic blood pressure from baseline to last value on treatment was observed for the ivabradine group (4.1 [16.0] mm Hg) than for the placebo group (2.0 [16.2] mm Hg). This was corroborated by adverse event reporting of “BP inadequately controlled” in patients who were previously known to be hypertensive (7.1% [4.2%PY], 6.1% [3.6%PY]). Blood pressure monitoring during therapy is recommended. The Division is interested in examining outlier responses carefully during the medical review.
7. Fetal toxicity risk. Ivabradine is considered to pose a possible risk of fetal toxicity: in rats, ivabradine was associated with cardiac teratogenicity and a higher incidence of neonatal mortality (at exposure levels similar to those in patients at the highest tolerated dose); in rabbits, ectrodactylia was observed (at exposures 15 to 34 times higher than therapeutic doses).

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:

### **Clinical Pharmacology**

1. Please submit pharmacokinetics, pharmacodynamics, and laboratory datasets (specifically serum creatinine measurements) in electronic format (not NONMEM files) for the following studies: CL1-001, CL1-002, CL1-003, CL1-004, CL1-029, CL1-039, CL1-040, PKH-001, PKH-003, PKH-004, PKH-005, PKH-006, PKH-010, CL2-006, CL2-009, CL2-030, CL2-047, CL2-062. We have not been able to locate the study electronic datasets in the submission. Please clarify if these have been submitted along with their location in the submission. If they are not part of the existing submission other than as part of NONMEM files, please submit them by 09/01/2014 to facilitate review.
2. Please submit a table listing studies and the bioanalytical methods used. If possible crosslink with validation reports and bioanalytical reports from the study.
3. The define files for NP27189 datasets ddidm-pl.xpt and mergeable-ddidmpl.xpt do not correctly identify study numbers. Please submit corrected define files and/or datasets.
4. Based on report NP08547 studies CL1-16257-001, CL1-16257-002, PKH-16257-001, PKH-16257-003, and CL1-16257-042 were used for the Pop-PK analysis. However, the 'define' file shows variable name STU (study number) 41 for CL1-41. Please clarify whether the nonmem ready dataset provided used study CL1-16257-042 as specified in the report or CL1-41 as mentioned in the 'define' file. For report NP15444, six studies (CL2-16257-006, CL2-16257-009, CL2-16257-047, CL3-16257-017, CL3-16257-018, and CL3-16257-023) were used. The 'define' file did not provide details of variable

names 'STUD' or 'STU'. Please confirm the variables for 'STU' in the corresponding dataset.

### **Clinical**

1. Please submit the following analyses from SHIFT alone, BEAUTIFUL alone, SIGNIFY alone (when available), and then all three studies integrated:
  - a. Kaplan Meier analyses of time to first occurrence of SBP or DBP > 120/80, 140/90, and 160/100.
  - b. Shift tables showing patient shifts between these various JNC-7 subcategories, including those who shift from or into the normal category at baseline, as well as those who shift to and from the elevated blood pressure categories during the trial (using highest recorded pressures for the categorical analyses).
  - c. Cumulative function plots of baseline systolic blood pressure, maximal systolic blood pressure during the trial (on the same plot as the baseline SBP curve), and maximal change from baseline systolic blood pressure during the trial.
  - d. Cumulative function plots of baseline diastolic blood pressure, maximal diastolic blood pressure during the trial (on the same plot as the baseline DBP curve), and maximal change from baseline diastolic blood pressure during the trial.
2. Analysis of SHIFT's primary and secondary efficacy outcomes in patients who would not have qualified for device therapy according to the 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities
3. Analysis of the SHIFT's primary and secondary efficacy outcomes among those few patients who did have indwelling ICD, CRT, or CRT-D devices during the course of the trial.
4. Analysis of SHIFT serious adverse events and adverse events including the two Polish sites that were excluded from the trial.
5. For all analyses requested above (#1-4), please also submit the SAS codes and datasets used to generate the results, if applicable.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. The Postmarketing Experience subsection should NOT include (b) (4)  
[REDACTED]
2. The regulatory statement required for (b) (4) must be included per 21 CFR (b) (4).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 16, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). 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.

### **PEDIATRICS**

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Cardiovascular and Renal Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

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/  
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NORMAN L STOCKBRIDGE  
08/25/2014



NDA 206143

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Amgen  
Attention: Christine Kubik  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
FAX: (805) 480-1330

Dear Christine Kubik:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ivabradine 5mg and 7.5mg film coated tablet.

We will be performing methods validation studies on Ivabradine 5mg and 7.5mg film coated tablet, as described in NDA 206143.

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

**Method, current version**

- Drug substance assay ( (b) (4) )
- Drug substance impurities (HPLC)
- Drug substance R isomer content (HPLC)
- Drug product assay and impurity (HPLC)

**Samples and Reference Standards**

- 2 g drug substance ivabradine hydrochloride
- 2 x 500 mg drug reference standard ivabradine hydrochloride (S 16257)
- 50 mg drug reference standard D
- 50 mg of drug substance selectivity batch reference standard
- 50 mg reference standard S 16260-2 (b) (4)
- 100 Ivabradine 5mg tablets
- 100 Ivabradine 7.5mg tablets

**Equipment**

- 1 column (b) (4) particle size
- 1 column (b) (4) particle size

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

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
645 S Newstead  
St. Louis, MO 63110

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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MICHAEL L TREHY  
08/18/2014



NDA 206143

## INFORMATION REQUEST

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ivabradine, 5 and 7.5 mg tablets.

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We request a prompt written response, within one week, in order to continue our evaluation of your NDA.

- A. Provide data on the physicochemical properties (e.g., solubility profile, melting point, hygroscopicity, and intrinsic dissolution) for all of the potential solid state forms of ivabradine hydrochloride drug substance. If there are clear differences in these physicochemical properties (e.g., low solubility at the physiologically relevant pH), then you should provide justification for the lack of impact of any observed differences on the bioavailability of the drug product.
- B. We acknowledge your proposal to use disintegration in lieu of dissolution testing. Note that if no data are provided to support the superior discriminating ability of disintegration over dissolution testing (see also comment C), you need to provide data supporting an adequate (discriminating) dissolution method for your proposed product.
- C. Provide data showing the superior discriminating capability of disintegration testing. The testing conducted to demonstrate the discriminating ability of this test should compare the dissolution profile and disintegration time of the drug product manufactured under target conditions vs. products intentionally manufactured with meaningful variations (i.e., +/- 10-20% outside established specification ranges) for the most critical formulation and manufacturing parameters.
- D. Provide disintegration values of all the batches tested in pivotal phase 3 clinical trials.
- E. In order to facilitate the review of the (b) (4) designation claim, provide sufficient information answering to the following questions:

## 1. Determination of the Drug Substance Class

- What are the highlights of the chemistry and physical-chemical properties of the drug substance?
- What is the nature of the drug substance (acid, base, amphoteric, or neutral)? What is the dissociation constant, PKa of the drug substance?
- What is the solubility profile of the drug substance under physiological pH conditions (i.e., pH range (b) (4) at 37°C in aqueous media)?
- Was the buffer solution's pH verified after the addition of the drug substance to the buffer?
- What type of method was selected to evaluate the equilibrium solubility of the drug substance? What are the specific experimental testing conditions?
- What analytical method was used to determine the concentration of the drug substance in the selected buffers (or pH conditions)? What data support the validation of the assay?
- What are the solubility pH profile results (individual, mean, standard deviation, coefficient of variation, and graphics)?
- Is the highest dose strength of the proposed drug-product soluble in 250 ml of aqueous media over the pH range of (b) (4)?
- Is the overall solubility information supportive of a (b) (4) classification for the drug substance?
- Were five pH conditions used to define the solubility pH profile? How many replicate determinations of solubility of the drug substance at each pH condition were performed?
- What type of buffer solutions were used to define the solubility profile? What are the compositions of the buffer solutions? How they were prepared?

## 2. Determination of Drug Substance Permeability Class

- What approach was used to determine the permeability class of the drug substance (i.e., *in vivo mass balance or absolute BA or intestinal permeability*)? If more than one method was used to demonstrate permeability classification, what are the other approaches?
- For human pharmacokinetic approaches, which approach was selected (i.e., *mass balance and/or absolute BA*)? What is the information describing the study design, methods, results, etc?
- For the intestinal permeability approaches, which method was selected (i.e., 1) *in vivo intestinal perfusion studies in humans*; 2) *in vivo or in situ intestinal perfusion studies using suitable animal models*; 3) *in vitro permeation studies using excised human or animal intestinal tissues*; or 4) *in vitro permeation studies across a monolayer of cultured epithelial cells*) and what is the rationale for its selection?
- Is the drug substance being testing a passively transported drug? What is the information supporting this determination?
- Was a linear relationship between the dose and measures of bioavailability (*humans*) demonstrated?
- Was there a lack of dependency of the measured *in vitro* permeability of the test article on initial drug concentration or transport direction (*no difference in the rate*)

*of transport between the apical-to-basolateral and basolateral-to-apical direction)* using a suitable in vitro cell culture method. What is the supportive information?

- For the in vivo-human perfusion studies, in vivo or in situ-animal intestinal perfusion studies or in vitro cell culture methods, how many model drugs were used? What model drugs were selected and did they represent a range of absorption values? What are the permeability values for each model drug (mean, SD, CV) and what is the permeability class of each model drug?
- What information supports the suitability of the selected method (i.e., description of the study, criteria for the selected approach, analytical method, method used to estimate the extent of absorption, (*where appropriate, efflux potential*), results (individual, mean, SD, coefficient of variation), etc.)? Were the results tabulated? Was the suitability of the selected permeability method(s) adequately demonstrated?
- What drugs were selected as low and high permeability internal standards? What is the high permeability internal standard used for the permeability classification?
- What is the information supporting the (b) (4) permeability of the drug substance (*i.e., permeability methods permeability data on the test drug substance and internal standards (mean, SD, & CV), data supporting classification and passive transport mechanism*)?
- What is the graphic representation of the extent of absorption as a function of permeability (*mean  $\pm$ SD or 95% CI*) with low/high permeability class boundary and selected internal standard(s). What is the rank-order relationship between test permeability values and the extent of drug absorption values?
- Is the overall information supporting a (b) (4) classification for the drug substance?

### 3. Gastric Stability

- What is the information supporting the stability of the drug substance/drug product in the GI tract?
- What are the experimental conditions used during the gastric stability experiments?
- Were simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) used to generate the chemical stability data or human fluid? What are the compositions of the SGF and SIF solutions?
- What is the validation information for the analytical method? What is a validated stability-indicating assay?
- What are the SGF and SIF stability results (mean, SD, CV)? Are the results tabulated?
- Is the overall information supportive of gastric stability?

### 4. Determination of the Dissolution Characteristics of the Drug Product

- What is the information describing the drug product used for dissolution testing (*i.e., batch/ lot No., expiry date, lot size, strength, etc.*)?
- What are the selected dissolution testing conditions (*i.e., apparatus, rotation speed, dissolution media, temperature, and volume*)?

- What is the sampling schedule? Does the sampling schedule adequately characterize the complete dissolution profile? Were twelve dosage units per experiment tested?
- What is the information supporting the validation of the dissolution methodology (robustness, etc.).
- What is the analytical method(s) used to determine the concentration of the drug in the dissolution samples? What is the validation information for the analytical method? Was it a validated assay?
- Was the dissolution of the drug product characterized in three different pH media?
- What are the compositions of the buffer solutions? How they were prepared? What are the dissolution characteristics in these media?
- What are the dissolution results (*i.e., individual, mean, SD, CV, and graphics*) in the different media? Are the results tabulated? Are the dissolution profile data reported in percent of label claim?
- Is the drug product showing fast dissolution in the different pH media? Is more than 85% of drug being dissolved in 15-30 minutes in each medium?
- Does the overall dissolution data support a rapid/fast dissolving designation for the drug product?

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

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/  
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NORMAN L STOCKBRIDGE  
08/11/2014

**From:** [Kubik, Christine](#)  
**To:** [Knight, Yvonne](#)  
**Subject:** RE: Information Request for NDA 206143 (Prompt Response)  
**Date:** Thursday, July 17, 2014 1:04:11 PM

---

Thank you, Yvonne for the voicemail and email. I confirm receipt of this Information Request.

Kind regards,  
Christine Kubik  
Senior Manager, Regulatory Affairs

---

**From:** Knight, Yvonne [mailto:[Yvonne.Knight@fda.hhs.gov](mailto:Yvonne.Knight@fda.hhs.gov)]  
**Sent:** Thursday, July 17, 2014 12:16 PM  
**To:** Kubik, Christine  
**Cc:** Knight, Yvonne  
**Subject:** Information Request for NDA 206143 (Prompt Response)  
**Importance:** High

Good afternoon Ms. Kubik,

Per my voicemail, We have an information request concerning Amgen's New Drug Application (NDA) for NDA 206143. We request a prompt response to this IR request no later than **Friday Noon July 18, 2014**.

1. Please clarify which drug substance sites are actually manufacturing the drug substance and which are only manufacturing the intermediates. (Note: The 365h and text differ)
2. Identify what type of testing is being done at both the Drug Substance and Drug Product sites (i.e. stability, release, etc...)

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

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

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/s/  
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YVONNE L KNIGHT  
07/17/2014



NDA 206143

**NDA ACKNOWLEDGMENT**

Amgen Inc.  
Attention: Ms. Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Blvd., Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

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: Ivabradine Tablets, 5 mg and 7.5 mg

Date of Application: June 27, 2014

Date of Receipt: June 27, 2014

Our Reference Number: NDA 206143

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 August 26, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Alexis Childers, RAC  
Regulatory Health Project Manager  
(301) 796-0442

Sincerely,

*{See appended electronic signature page}*

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

-----  
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/s/  
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EDWARD J FROMM  
07/15/2014



PNDA 206143

**GENERAL ADVICE**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your Pre New Drug Application (PNDA) file for Ivabradine.

We also refer to your June 12, 2014 submission, containing a general correspondence regarding the SIGNIFY study.

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

We agree that you do not need to include the preliminary results from the recently completed SIGNIFY trial in the NDA you plan to submit this month seeking approval to market ivabradine for treatment of heart failure. You intend to provide a safety update from the SIGNIFY trial at the Day 120 safety update and we would like for you to submit the latest version of the CSR at that time.

If you have any questions, please call Alexis Childers, Regulatory Project Manager at (301) 796-0442.

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/  
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NORMAN L STOCKBRIDGE  
06/19/2014



pNDA 206143

**MEETING MINUTES**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your Pre New Drug Application (PNDA) file for Ivabradine.

We also refer to the meeting between representatives of your firm and the FDA on January 22, 2014. The purpose of the meeting was to discuss the top-line results from your pivotal trial SHIFT.

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 Alexis Childers, Regulatory Project Manager at (301) 796-0442.

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  
Sponsor slides



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type C  
**Meeting Category:** Top-Line Results

**Meeting Date and Time:** January 22, 2014  
**Meeting Location:** White Oak, Bldg 22, Room 1313

**Application Number:** 206143  
**Product Name:** Ivabradine  
**Indication:** Reduction of the risk of [REDACTED] (b) (4)  
hospitalizations for worsening heart failure in patients with chronic  
heart failure [REDACTED] (b) (4)  
[REDACTED] in sinus rhythm and with heart rate  $\geq 70$  bpm, (b) (4)  
[REDACTED]  
or when beta-blocker therapy is contraindicated [REDACTED] (b) (4)

**Sponsor Name:** Amgen, Inc.

**Meeting Chair:** Robert Temple, M.D..  
**Meeting Recorder:** Alexis Childers, RAC

**FDA ATTENDEES**

*\*Office of Drug Evaluation I*

Robert Temple, M.D. Deputy Director

*\*Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D. Director

Stephen Grant, M.D. Deputy Director

Mary Ross Southworth, PharmD Deputy Director for Safety

Tom Marciniak, M.D. Clinical Team Leader

Martin Rose, M.D. Clinical Team Leader

Preston Dunnmon, M.D. Clinical Reviewer

Nhi Beasley, Pharm.D. Clinical Reviewer

Alexis Childers, RAC Sr. Regulatory Health Project Manager

Michael Monteleone, MS, RAC Sr. Regulatory Health Project Manager

Edward Fromm, R.Ph., RAC Chief, Regulatory Health Project Manager

*\*Office of Clinical Pharmacology*

Martina Sahre, Ph.D. Clinical Pharmacology Reviewer

Rajanikanth Madabushi, Ph.D. Clinical Pharmacology Team Leader

*\*Office of Biostatistics, Division of Biometrics I*

Steve Bai, Ph.D. Statistician

*\*Office of Scientific Investigations*

Sharon Gershon Pharm.D.  
\*Office of Surveillance and Epidemiology  
Tamra Meyer  
Somya Dunn

**EASTERN RESEARCH GROUP ATTENDEES**

Patrick Zhou Independent Assessor

**SPONSOR ATTENDEES**

***Amgen***

Dominique Bertin-Millet, MD	Executive Medical Director, Global Safety
Chao-Yin Chen, PhD	Senior Manager, Biostatistics
Lisa DiMolfetto, PhD	Director, Global Regulatory Affairs
Paul Eisenberg, MD, MPH	Senior Vice President, Global Regulatory Affairs and Safety
Laurence Gamelin, MD, MS, PhD	Medical Director, Global Safety Officer
Rekha Garg, MD, MS	Executive Director, Global Regulatory Affairs
Graham Jang, PhD, MBA	Medical Sciences Director, Clinical Pharmacology
Jae B. Kim, MD, FACC	Clinical Research Medical Director, Global Development
Christine Kubik	Senior Manager, US Regulatory Affairs
Arline Nakanishi, MS	Executive Director, Biostatistics
Rameshraj Palaparthi, PhD	Principal Scientist, Quantitative Pharmacology, Pharmacokinetics and Drug Metabolism
Rob Scott, MD	Vice President, Global Development
John Wisler, PhD, DABT	Scientific Director, Toxicological Sciences

***Servier***

Catherine Salvadori	International and Pre-submission Division Director, Worldwide Regulatory Affairs
Virginie Falte, MD, PhD	Project Director Ivabradine, Regulatory Affairs Manager USA, Worldwide Regulatory Affairs
Guys Lerebours, MD	Medical and Scientific Director, Cardiovascular Therapeutic Division
Fabienne Dominjon, MD	Project Manager, Cardiovascular Therapeutic Division
Sandrine Guilleminot, DEA	Manager, Biostatistics Department

***Consultant***



## 1.0 BACKGROUND

Ivabradine, developed by Les Laboratoires Servier, slows heart rate by modulating pacemaker activity in the sinus node. It is currently marketed in 64 countries for the treatment of chronic heart failure and in 100 countries for the treatment of angina. An application to market ivabradine in the USA has not been submitted. Amgen recently acquired the commercial rights for the USA and is proposing to submit an NDA in Q1 2014 for treatment of heart failure.

The results of a single large, randomized, placebo-controlled outcomes study entitled Systolic Heart Failure Treatment with the  $I_f$  inhibitor ivabradine Trial (SHIFT) will provide the primary support for the safety and efficacy of ivabradine for this indication. BEAUTIFUL, a phase 3 international, multicenter, randomized, double-blind, parallel group, placebo-controlled, long – term outcomes study assessing the effects of ivabradine on mortality and cardiovascular events in patients with stable coronary artery disease and left ventricular systolic dysfunction will provide supportive information.

The purpose of the meeting is to provide the Division with top-line results from the pivotal trial, SHIFT. A separate Pre-NDA meeting was held on January 23, 2014 and a CMC pre-NDA meeting was held on December 6, 2013

## 2.0 DISCUSSION

Amgen presented the attached slides. Highlights from the discussion are below.

### Opening Remarks:

The prevalence of heart failure (HF) is expected to increase significantly over the coming years. HF patients with higher heart rates have poorer prognoses than those with lower heart rates and so heart rate (HR) is a risk marker in heart failure. Slide 8 showed selected recent heart failure trials and registries and the mean or median heart rate. Amgen stated that a 5 beat decrement in HR was associated an 18% relative risk reduction in mortality of HF patients. Irrespective of medications the subjects in HF trials were taking (such as beta-blockers), the mean heart rate in these trials is high.

Ivabradine inhibits  $I_f$  and reduces heart rate. Heart failure, angina and CAD have been studied in the clinical program. To date SHIFT is the largest heart failure outcomes trial ever conducted. The NDA will contain 70 clinical studies including the SIGNIFY trial, an ongoing CV outcomes trial in patients with CAD. It will also include a robust PK/PD dossier. Based on the PK/PD studies, the sponsor chose 7.5 mg BID as the highest dose to study in Phase 3 because higher doses produced modest additional heart rate reduction, and reversible phosphenes were observed. Refer to slide 14 for other notable clinical pharmacology characteristics. Of note though, ivabradine is rate dependent--the faster the HR, the greater the effect of ivabradine on HR; it has less effect at lower heart rates.

### SHIFT trial:

The SHIFT trial included three main trial committees: the Executive Committee, reviewing the overall conduct; the Data Monitoring Committee; and the Endpoint Validation Committee,

reviewing all adjudications. Patients had to have been admitted to the hospital within the last 12 months and on optimal therapy to be eligible to enroll. The initial dose was 5 mg bid, which was titrated up to 7.5 mg bid or down to adjust for heart rate (slide 22). Exclusion criteria included having a pacemaker operating more than 40% of the time, permanent atrial fibrillation (because the drug only works on the sinoatrial node - slide 23). The primary composite endpoint was time to CV death or first hospitalization for worsening heart failure. Amgen feels that endpoint ascertainment was designed to ensure that events were not missed (slide 25) and all events were meaningful. Servier developed the criteria for the endpoints prior to publication of the draft FDA Standard End Point Definitions for Cardiovascular Trials yet they are very similar (slide 24). Baseline characteristics were balanced between the treated and placebo group. The majority of patients were on background therapy, mainly with beta blockers and ACEIs/ARBs, diuretics, etc. (slide 29). Of the 90% of patients randomized who were taking beta blockers, at least 50% were taking target daily dose and approximately 25% were not taking the target daily dose.

#### SHIFT Results (slides 32-56):

According to Amgen, the effect of ivabradine on heart rate is observed by 4 weeks and the effect is sustained throughout the trial (the effect at trial end was ~ -8 bpm). There was a significantly reduced risk of the primary endpoint of CV death or first hospitalization for worsening heart failure; the effect was primarily driven by a 26% reduction in first hospitalization for heart failure. CV death trended in the right direction, but it was not statistically significant. The effects across most pre-specified secondary endpoints as well as pre-specified subgroups were consistent with the primary endpoint. In a post-hoc analysis, there was a 25% reduction in total hospitalizations. In a total time approach, it took 47% longer for a second hospitalization if on ivabradine and 29% longer to have a third hospitalization. Ivabradine also reduced the risk of hospitalizations from any cause [any cause 15% reduction, cardiovascular 16% reduction, heart failure (pre-specified endpoint) 25% reduction and hospitalization other than heart failure 8% reduction]. There were no differences in geographic regions on the primary endpoint. Quality of life was improved.

#### BEAUTIFUL Trial

Amgen indicated that safety data will come from the BEAUTIFUL trial which was initiated prior to SHIFT. The trial enrolled patients with CAD and left ventricular systolic dysfunction whereas SHIFT enrolled patients with chronic heart failure of any etiology except for congenital and valvular. Slide 60 shows the differences between SHIFT and BEAUTIFUL. The main differences were in the inclusion criteria, LVEF, NYHA class, heart rate, worsening heart failure and the primary endpoint. Baseline characteristics were different between the two trials. There was a trend but no difference between treated and placebo on the primary composite endpoint of CV death and hospitalization for acute MI and new onset/worsening heart failure.

An analysis of BEAUTIFUL that included only the subset of subjects with heart rate  $\geq 70$  bpm at baseline showed similarities in outcomes to those observed in SHIFT; i.e., there appeared to be a reduction in the risk of CV death or hospitalization for worsening heart failure. There were similar types and frequencies of treatment-emergent AEs in the two trials and ivabradine appeared to be similarly well tolerated.

### **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.

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

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

#### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of 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, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

#### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission

[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

**MANUFACTURING FACILITIES**

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

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

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

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

Corresponding names and titles of onsite contact:

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

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

pNDA 206143  
Top- Line Meeting Minutes

**5.0 ACTION ITEMS**

None

**6.0 ATTACHMENTS AND HANDOUTS**

Sponsor presentation entitled "Pre-NDA Meeting January 22, 2014"

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/s/  
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ROBERT TEMPLE  
02/20/2014



PNDA 206143

**MEETING MINUTES**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your Pre New Drug Application (PNDA) file for Ivabradine.

We also refer to the meeting between representatives of your firm and the FDA on January 23, 2014. The purpose of the meeting was to discuss data currently available to support a NDA submission.

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 Alexis Childers, Regulatory Project Manager at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Meeting Minutes  
Sponsor slides



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** January 23, 2014, 9:00 am EST  
**Meeting Location:** White Oak Building 22, Conference Room: 1315

**Application Number:** 206143  
**Product Name:** Ivabradine  
**Indication:** reduction of the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) in sinus rhythm and with heart rate  $\geq 70$  bpm. (b) (4) or when beta-blocker therapy is contraindicated (b) (4).

**Sponsor Name:** Amgen, Inc.

**Meeting Chair:** Norman Stockbridge, M.D., Ph.D.  
**Meeting Recorder:** Alexis Childers, RAC

**FDA ATTENDEES**

*\*Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Stephen M. Grant, M.D.	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Tom Marciniak, M.D.	Clinical Team Leader
Martin Rose, M.D.	Clinical Team Leader
Preston Dunmon, M.D.	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Jean Wu, M.D., Ph.D.	Pharmacologist
Alexis Childers, RAC	Sr. Regulatory Health Project Manager
Edward Fromm, R.Ph., RAC	Chief, Regulatory Health Project Manager

*\*Office of Clinical Pharmacology*

Martina Sahre, Ph.D.	Clinical Pharmacology Reviewer
Sreedharan Sabarinath, Ph.D.	Clinical Pharmacology Reviewer
Rajanikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader

*\*Office of Biostatistics, Division of Biometrics I*

Steve Bai, Ph.D. Statistician

*\*Office of Scientific Investigations*

Sharon Gershon Pharm.D. OSI Reviewer, Pharmacologist

*\*Office of Surveillance and Epidemiology*

Tamra Meyer, PHD, MPH Epidemiologist  
Somya Dunn, MD Risk Management Analyst, DRISK  
Lisa Khosla, PharmD, MHA Team Leader, DMEPA

**EASTERN RESEARCH GROUP ATTENDEES**

Patrick Zhou Independent Assessor

**SPONSOR ATTENDEES**

**Amgen**

Diane Androvich, MS Senior Manager, Statistical Programming  
Dominique Bertin-Millet, MD Executive Medical Director, Global Safety  
Chao-Yin Chen, PhD Senior Manager, Biostatistics  
Lisa DiMolfetto, PhD Director, Global Regulatory Affairs  
Michael Eschenberg, MS Director, Biostatistics  
Rachel Feast Manager, Global Study Operations – Data Management  
Laurence Gamelin, MD, MS, PhD Medical Director, Global Safety Officer  
Rekha Garg, MD, MS Executive Director, Global Regulatory Affairs  
Graham Jang, PhD, MBA Medical Sciences Director, Clinical Pharmacology  
Jae B. Kim, MD, FACC Clinical Research Medical Director, Global  
Development  
Christine Kubik Senior Manager, US Regulatory Affairs  
Arline Nakanishi, MS Executive Director, Biostatistics  
Barrie Nelson, LSRC Director, Biomedical Data Stewardship  
Rameshraj Palaparthi, PhD Principal Scientist, Quantitative Pharmacology,  
Pharmacokinetics and Drug Metabolism  
Rob Scott, MD Vice President, Global Development  
John Wisler, PhD, DABT Scientific Director, Toxicological Sciences

**Servier**

Catherine Salvadori International and Pre-submission Division Director,  
Worldwide Regulatory Affairs  
Virginie Falte, MD, PhD Project Director Ivabradine, Regulatory Affairs Manager  
USA, Worldwide Regulatory Affairs  
Guys Lerebours, MD Medical and Scientific Director, Cardiovascular  
Therapeutic Division  
Fabienne Dominjon, MD Project Manager, Cardiovascular Therapeutic Division  
Sandrine Guilleminot, DEA Manager, Biostatistics Department

## BACKGROUND

Ivabradine, developed by Les Laboratoires Servier, slows heart rate by modulating pacemaker activity in the sinus node. It is currently marketed in 64 countries for the treatment of chronic heart failure and in 100 countries for the treatment of angina. An application to market ivabradine in the USA has not been submitted. Amgen recently acquired the commercial rights for the USA and is proposing to submit an NDA in Q1 2014 for treatment of heart failure.

The results of a single large, randomized, placebo-controlled outcomes study entitled Systolic Heart Failure Treatment with the I<sub>f</sub> inhibitor ivabradine Trial (SHIFT) will provide the primary support for the safety and efficacy of ivabradine for this indication. BEAUTIFUL, a phase 3 international, multicenter, randomized, double-blind, parallel group, placebo-controlled, long – term outcomes study assessing the effects of ivabradine on mortality and cardiovascular events in patients with stable CAD and left ventricular systolic dysfunction will provide supportive information.

The purpose of the meeting was to discuss the content and format for the NDA submission. A separate Top-Line Results meeting was held on January 22, 2014 and a CMC pre-NDA meeting was held on December 6, 2013.

## 1.0 DISCUSSION

### CLINICAL

1. As outlined in Section 3.2, the SHIFT study is a phase 3, international, double-blind, randomized, placebo-controlled, multicenter study in 6558 subjects with symptomatic chronic heart failure with systolic dysfunction. Subjects received ivabradine or placebo on top of stable guideline-recommended therapies, which included a beta-blocker, an ACE inhibitor or ARB, a mineralcorticoid receptor antagonist, and a diuretic. All subjects were expected to be receiving target evidence-based beta-blocker doses or the investigator was to document a reason why the subject was not at target dose (Swedberg et al, 2012; Swedberg et al, 2005). SHIFT demonstrated that treatment with ivabradine significantly reduces cardiovascular mortality or hospitalization for worsening heart failure (primary composite endpoint) compared to placebo. The absolute risk reduction was 4.2% and the estimate of the hazard ratio was 0.82 (95% CI [0.75; 0.90],  $p < 0.0001$ ), corresponding to a relative risk reduction of 18%, a result that is clinically meaningful and statistically significant.

It is Amgen's position that SHIFT, as a large, well-conducted multicenter study showing a significant and robust effect on clinical outcomes in patients with chronic heart failure, meets the FDA's requirements for new drug approval based on a single well-controlled outcomes trial.

*Does the FDA agree?*

**FDA Preliminary Comments:** Per our response to your Question 6 in the minutes of our meeting with Servier on 15 November 2011:

*Whether the SHIFT trial provides sufficient evidence to support the proposed indication is dependent on our review of the data in this trial. As we indicated above, a critical element in our review will be our determination of the quality of the data you submit. We do note that you plan to submit in the NDA only one adequate clinical trial to provide evidence of safety and efficacy whereas our guidance states that generally two trials are necessary for approval. We also note that in another study conducted in a population similar to the one enrolled in SHIFT (patients with stable class 2-3 HF and CAD), the incidence of the composite of CV mortality, hospitalization for heart failure and hospitalization for acute MI slightly favored placebo (844 vs. 832) and more CV deaths were observed in ivabradine subjects than placebo subjects (469 vs. 435). Further, SHIFT was performed mostly in Eastern Europe (4243 subjects of 6505 total) where medical practice and available therapeutic options differ from those in the United States. Finally, the benefit of ivabradine on cardiovascular events appears to be driven mainly by a reduction in hospitalization for worsening heart failure among subjects who were not on full doses of  $\beta$ -blockers despite unequivocal evidence that  $\beta$ -blockers reduce mortality. We think it likely that if approved, ivabradine will be indicated only for heart failure patients in sinus rhythm and a heart rate  $\geq 70$  bpm despite maximally tolerated doses of  $\beta$ -blockers.*

The Division's position on this subject is unchanged, and we understand from the discussion at our 2011 meeting Servier intended only to seek approval for ivabradine as an adjunct to maximally tolerated  $\beta$ -blocker therapy in HF<sub>r</sub>EF patients with a heart rate  $\geq 70$  BPM.

Among potential review issues, we note that under CFR 312.120 and CFR 314.106, if an application is based solely on foreign clinical data, it must (a) meet the US criteria for marketing approval, (b) show that (i) the foreign data are applicable to the US population and the US medical practice, (ii) the studies have been performed by clinical investigators of recognized competence (as described in CFR 312.120), and (c) be able to be validated by FDA through an on-site inspection or other appropriate means. Also, the clinical trial sites must be documented to have had IRB oversight and must have retained copies of informed consent forms signed by all subjects.

**Discussion during meeting:** No further discussion.

2. The planned content of the clinical portions of the NDA is outlined in Section 3.7. Amgen proposes to provide a summary of clinical safety (SCS) that includes results from
  - the pivotal outcomes study, SHIFT, which provides long-term safety data from > 6500 patients with chronic heart failure
  - five phase 2 studies in chronic heart failure (presented individually due to differences in dosing regimens and study designs)
  - an Integrated Summary of Safety (ISS) report summarizing a pooled analysis of 1 phase 2 and 8 phase 3 angina studies available as of May 2010. Results of 3 additional angina studies (a single-dose study [CL2-16257-006], a study in only Asian subjects [Study

CL3-16257-064], and a recently completed study [Study CL3-16257-068]) will be summarized separately in the SCS.

- the BEAUTIFUL study, which provides long-term safety data from > 10,000 patients with stable CAD and left ventricular systolic dysfunction
- Summaries of safety results from additional smaller studies will be provided as described in Section 3.7.2.1.

Amgen does not plan to integrate safety data across the chronic heart failure, CAD, and angina patient populations because of the differences in patient populations, as well as differences in study design. In addition to the SCS, Amgen will provide the following documents in the NDA submission to support the FDA's review of the safety of ivabradine:

- clinical study reports (CSRs) for 70 completed ivabradine clinical studies in which over 24,000 subjects were treated, including the CSR for the pivotal chronic heart failure study, SHIFT
- all 10 Periodic Safety Update Reports (PSURs), which summarize > 1,600,000 patient-years of exposure in the postmarketing setting from the international birth date (25 October 2005) through 25 October 2013

*Does the FDA agree with this proposed scope?*

**FDA Preliminary Comments:** Yes. Please also summarize the information in the 10 PSURs into one report.

Please provide an update on the status of SIGNIFY (CL-16257-083). If this study is already unblinded, or will be by the time of the 120-day update, you should summarize its pertinent safety findings.

**Discussion during meeting:** No further discussion.

3. The safety narratives to be provided in the NDA are discussed in Section 3.7.2.1. For the outcomes studies, SHIFT and BEAUTIFUL, safety narratives will be provided for
  - treatment-related serious adverse events
  - unrelated serious adverse events that were not pre-specified events (as defined in the study protocol; see Section 3.2.2 [SHIFT] and Section 3.5 [BEAUTIFUL]) and were either
    - life-threatening OR
    - events of interest OR
    - led to discontinuation
  - non-serious adverse events leading to discontinuation.

For non-outcomes studies, Amgen will provide safety narratives for serious adverse events and all adverse events leading to discontinuation.

*Does the FDA agree with the provision of narratives as described?*

**FDA Preliminary Comments:** Please also submit safety narratives for patients experiencing laboratory adverse events, total bilirubins  $\geq 2X$  the ULN or transaminases  $\geq 3X$  the ULN.

**Discussion during meeting:** The sponsor stated that no evidence of drug-induced liver injury (DILI) has been found in clinical or preclinical studies nor have there been post-marketing reports of DILI, hepatic transplants for DILI, or death from DILI. If true, then the documentation requested by the Division may be brief. The sponsor and the Division agreed that narratives from both SHIFT and BEAUTIFUL would be submitted for subjects who had transaminase elevations  $\geq 3X$  ULN and total bilirubin  $\geq 2X$  ULN, and for subjects who experienced hepatic laboratory abnormalities that were considered to be adverse events by the investigator. CRFs and adverse event reports for all of these subjects should be also submitted in the NDA.

Liver associated enzyme abnormalities should be evaluated and categorized according to Guidance for Industry, Drug-Induced Liver Injury: Premarket Clinical Evaluation (July 2009) (<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>).

**Post Meeting Note** –the Divisions expects that the hepatic safety of your drug has been assessed as suggested in FDA’s Guidance on drug-induced liver injury. Specifically, we expect that appropriate laboratory sampling has been obtained during your development program to perform the categorical analyses for hepatic injury that are discussed in this document. Please refer to this guidance as you prepare your categorical analyses of liver enzyme shifts from both SHIFT and BEAUTIFUL. We recall that you may have stated that liver enzyme assessments from SHIFT were not systematically acquired. If there was indeed no systematic assessment of hepatic laboratory safety in SHIFT, it will be important that you submit a comprehensive analysis of hepatic safety per the guidance in an appropriately integrated dataset from other trial sources.

4. Consistent with PSUR #10, Amgen proposes 25 October 2013 as the data cut-off date for the NDA. Amgen proposes to submit a 120-day safety update report covering the period between 26 October 2013 and 25 January 2014, which will include new information from postmarketing data and any new important information from Studies CL3-16257-067 (long-term ophthalmic safety) and (b) (4) (Section 3.7.2.2).

*Does the FDA agree with the proposed data cut-off dates for the NDA and the 120-day safety update report?*

**FDA Preliminary Comments:** Yes.

**Discussion during meeting:** No further discussion.

5. As described in Section 3.7.2.1 and in accordance with 21 CFR 314.50(f)(2), Amgen proposes to provide case report forms (CRFs) from the pivotal SHIFT study for all subjects who had discontinuations/withdrawals related to adverse events and for all subjects who died; the entire casebook for these subjects will be provided. These CRFs will be hyperlinked within the electronic Common Technical Document (eCTD) at the page level.

*Does the FDA agree with the proposal for inclusion of CRFs?*

**FDA Preliminary Comments:** Please also submit CRFs for all subjects who discontinue/withdraw for any reason, are lost to follow-up, experience SAEs that result in hospitalization, or adverse events involving prolongation of electrocardiographic intervals, conduction system disturbances, or arrhythmias. Please note that CRFs include all forms or documents with clinical information collected for the trial, including SAE reports and “adjudication packages” (see Response 4 below), not just documents labeled as “case report forms”.

**Discussion during meeting:** The sponsor asked if the requested CRFs are for subjects who discontinued or withdrew from the study or who discontinued study drug. The Division would like CRFs from those who discontinued study drug. The sponsor indicated that the CRFs are electronic and in English. The sponsor was to verify that the CRFs are text searchable. See also our comments on CRF/AE submissions in Question 3 above.

The Division requested a dataset with the following seven variables for both SHIFT and BEAUTIFUL:

- Study ID
- Unique subject ID
- A variable that indicates subjects with submitted narratives, CRF, SAE, discontinued IP, and adjudication package. (*Post meeting note: the dataset should only include subjects that have one these submitted.*)

The Division also requested a table that hyperlinks these subjects to the respective narrative, CRF, SAE report, and adjudication package.

The Division requested that no dataset be split. If the sponsor has any questions, contact the ESUB team. The sponsor may also engage the Division prior to the NDA submission to ensure the datasets are acceptable.

The Division asked for a RANK analysis for all cause death with no censoring, an analysis for time to first death and all cause hospitalization, and an analysis of incomplete follow-up (i.e., the status of an event that is part of the primary endpoint is unknown).

The sponsor confirmed that adverse events that were also endpoint events were captured on the AE CRF and the endpoint event CRF.

**Post Meeting Note:** Amgen emailed the following comment on February 3: In addition to the Holter ECG substudy, the BEAUTIFUL study has an Echocardiography / NT-proBNP

sub-study. However, there is no specific assessment of safety performed on patients in this sub-study. Therefore, Amgen proposes not to submit datasets for this sub-study. Amgen will submit the Echocardiography / NT-proBNP sub-study from the Shift study. Amgen asked if the Division is in agreement with the proposal.

In an email response on February 6, 2014 the Division responded: There is much overlap between SHIFT and BEAUTIFUL populations. Functional imaging and biomarker data for BEAUTIFUL should be submitted with the NDA.

6. As described in Section 3.7.1, Amgen proposes to support Agency review of the pivotal study, SHIFT, by submitting datasets that are most relevant to evaluate the chronic heart failure indication: the main study, the echocardiography/N-terminal prohormone of brain natriuretic peptide (NT-proBNP) substudy and the Holter electrocardiogram (ECG) substudy. Amgen does not plan to integrate the efficacy data from SHIFT with any other study, since SHIFT represents the single pivotal, phase 3, placebo-controlled study that was designed to evaluate outcomes in a heart failure population.

Amgen will also submit the main efficacy and safety datasets from BEAUTIFUL, a study designed to evaluate the efficacy of ivabradine in the treatment of CAD with left ventricular systolic dysfunction. Results from the BEAUTIFUL study provide long-term safety data on the use of ivabradine in patients with stable CAD and left ventricular systolic dysfunction, and a subgroup analysis from this study provides data to support the efficacy of ivabradine in a population of patients with heart failure (Section 3.5.2).

*Does the FDA agree with the proposed scope of the datasets to be provided?*

**FDA Preliminary Comments:** No. Please submit all datasets (CRT and analysis), and data define files. Submit all SAS programs used to generate the main tables and figures included in the SCS, and CSR for SHIFT and BEAUTIFUL. We prefer executable SAS programs. Please be prepared to submit additional SAS programs for analyses found in the SHIFT and BEAUTIFUL appendices.

**Discussion during meeting:** Amgen stated Servier never submitted datasets to the EMA and creating them is a lot of work. They would like to limit what data are submitted specifically to what is needed for the current proposed indication, mainly data from SHIFT and not BEAUTIFUL.

The Division stated that the applicant cannot choose the safety data that the Agency reviews. For example, there may be Holter data from BEAUTIFUL that shows changes in cardiac electrophysiology that would be pertinent to our review. The Division also clarified that all of the items in the preliminary responses are requested up front so that the application is easier to navigate. The Division and sponsor agreed to submit all of the CRTs and define files for SHIFT, including substudies, and BEAUTIFUL at the time of submission including Holter data. All define files will be submitted as PDF.

It was agreed that PRO data are not relevant to the claim, so no datasets are required, but EQ5 and KCCQ information will be submitted.

7. As described in Section 3.7.1, SHIFT and BEAUTIFUL were not planned prospectively to adopt Clinical Data Interchange Standards Consortium (CDISC) standards. Amgen proposes to submit datasets in the legacy case report tabulation (CRT) format. For each individual study, Amgen proposes to supply a dataset package containing the following deliverables:
- blank CRF annotated with CRT names and variables
  - CRTs in SAS V5 transport file format
  - a define.pdf file describing the content and structure of all submitted CRTs
  - CRT reviewer's guide to assist review
  - sample SAS programs for key analyses

In addition, Amgen proposes to have a Type C meeting after the submission of the NDA to go over the structure and content of the final dataset packages to facilitate the FDA's review of the heart failure NDA submission.

*Does the FDA agree with this proposal?*

**FDA Preliminary Comments:** Please see comment 6.

**Discussion during meeting:** No further discussion.

8. The clinical pharmacology of ivabradine or its major metabolite was evaluated in 34 phase 1 studies conducted in healthy volunteers, subjects with renal or hepatic impairment, and subjects with asthma (Table 32 in Appendix 4), and in 25 phase 2 or phase 3 studies in patients with chronic heart failure, CAD, angina, and other heart conditions (indicated within Table 40 in Appendix 2). For all of these studies, the key results pertinent to the clinical pharmacology of ivabradine will be summarized in the NDA and the study reports included. In addition, as discussed in Section 3.7.3.2 Amgen proposes to submit 7 non-linear mixed effects modeling (NONMEM) datasets that include pharmacokinetics (PK) or PK/pharmacodynamics (PD) data from 23 of these studies: 13 phase 1, 4 phase 2, and 6 phase 3 studies (listed in Table 38). Amgen considers that datasets for these studies are appropriate for the submission because they include

(1) data from the initial phase 1 studies characterizing the safety, tolerability, PK and PD of ivabradine in healthy adults;

(2) studies characterizing notable drug-drug interactions for ivabradine, such as those involving ketoconazole and josamycin; and

(3) data supporting the development of a population PK/PD model for ivabradine, including an analysis using data from SHIFT.

The format for submission will be in accordance with the FDA's guidance, *Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product*

*Applications and Related Submissions Using eCTD Specifications (2008)*. Data Definition Table files will be included.

*Does the FDA agree?*

**FDA Preliminary Comments:**

- (1) Your proposal to submit full clinical pharmacology reports (study reports and the relevant data sets) for the 34 phase I studies and in 25 phase 2 or phase 3 studies is acceptable.
- (2) We also notice that there is DDI characterization in healthy volunteers and in the target population for some drugs. You should compare and contrast the findings from these studies and also identify which of those studies will support the labeling instructions.
- (3) While it is acceptable to submit the population PK/PD datasets as proposed, we strongly encourage you to consolidate the most important analyses.

Please refer to the eCTD guidance, “*Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using eCTD Specifications (2008)*” and all eCTD Guidance and Specifications located on the eCTD website:-  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>, for submission.

**Discussion during meeting:** The sponsor is trying to produce the most relevant datasets as a number of the studies are considered legacy trials (legacy trials were defined by the sponsor as those that were done a long time ago). Amgen plans to submit 7 NONMEM datasets covering key clinical pharmacology data, 10 phase 2/3 studies, 13 phase 1 studies supporting the development of the model (see attached), and 13 additional datasets from DDI studies, food effect and hepatic/ renal impairment ADME studies, mostly in healthy volunteers which will affect labeling.

The Division agreed with the plan, but asked whether Amgen would agree to submit data for remaining studies if the Division were to ask for it. The sponsor agreed. Amgen was also asked to compare results from healthy subjects to patients when there are studies done in both populations. Amgen agreed to the comparison and is planning to submit all study reports, including those where individual data sets will not be submitted.

Regarding consolidation, the sponsor feels they may not be able to consolidate datasets further as they are tied to analysis reports. The Division agreed that Amgen can submit but stated that the Division is mostly interested in the final analyses that are pertinent to regulatory action or labeling, instead of all the interim analyses that were conducted at different stages of development. The sponsor should also ensure that all NONMEM datasets can be merged with little data preparation (i.e. use the same data formatting throughout).

The Division also requested a continuous Table of Contents for all study reports submitted with the NDA, with functional links.

9.

(b) (4)

**Discussion during meeting:** No further discussion.

10. In a 2011 pre-IND meeting with Les Laboratoires Servier, the FDA invited the sponsor to submit for the FDA's review information characterizing the effect of ivabradine on the QT interval. As noted in Section 3.7.2.1, Amgen has provided a summary of QT data as a presubmission to NDA 206143 (31 October 2013, #0007).

*Does the FDA agree that the effect of ivabradine on the QT interval has been adequately characterized in the information previously submitted and that a TQT study is not required?*

**FDA Preliminary Comments:** A TQT study is not required because we do not consider that it will adequately assess ivabradine's proarrhythmic liability because of the confounding effects of the large decrease in heart rate.

**Discussion during meeting:** No further discussion.

#### **CLINICAL/ NONCLINICAL**

11. Amgen has assessed the potential for drug abuse with ivabradine in receptor-binding studies, studies of the distribution of radiolabeled ivabradine in rat, safety pharmacology and reproduction studies in rat, and single- and repeated-dose studies in rat and dog ( Section 4.2.4), and through analysis of adverse events reported in clinical studies (Section 3.7.2.1). Based on the nonclinical and clinical data, Amgen considers that the abuse potential of ivabradine is negligible.

*Does the FDA agree that Amgen has adequately assessed the abuse potential of ivabradine?*

**FDA Preliminary Comments:** Pending review, it appears that pharmacology and toxicology studies summarized in the meeting package do not raise a significant concern for a potential abuse of ivabradine if there has been no evidence of abuse potential in human. However, you need to provide clinical data demonstrating the lack of withdrawal-type and rebound behavior, as well as any abuse behavior, and address the abuse potential in the NDA submission.

**Discussion during meeting:** No further discussion.

## REGULATORY

12. As discussed in Section 3.8, based on the significant reduction in cardiovascular mortality or hospitalization for worsening heart failure observed in SHIFT, Amgen believes that ivabradine provides an important additional therapy for patients with heart failure and will request a priority review of the NDA.

*Can the FDA provide feedback on whether priority review will be considered?*

**FDA Preliminary Comments:** Assuming that your data package supports a positive filing decision, the Division will consider a priority review for the proposed indication.

**Discussion during meeting:** The Division emphasized that a complete package is required in all instances but that submissions deficient in any aspect were especially problematic for NDAs classified as priority because of the shorter timelines. We will not file an NDA submitted without all the necessary information or in which the necessary information cannot be located.

Amgen indicated that Servier is in the process of collecting financial disclosure information for all SHIFT investigators and have obtained information for about 70% of the investigators so far. The Division told Amgen that an applicant is required to provide financial disclosure information in a marketing application or certify that it acted with due diligence to obtain necessary information but was unable to do so and state the reason (21 CFR § 54.4). FDA may refuse to file any marketing application supported by covered clinical studies that does not contain, for each clinical investigator who is not an employee of the sponsor, a certification that no financial interest or arrangement specified in 54.4(a)(3) exists, a disclosure statement identifying the specified financial interests or arrangements and the steps taken to minimize bias, or a certification that the applicant has acted with due diligence to obtain the required information but was unable to do so and stating the reason (21 CFR § 54.4(c)). For additional details Amgen is referred to FDA's Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>).

The Division indicated that it is likely to convene an Advisory Committee to discuss the application.

### Additional FDA Comments:

1. Please submit in the original NDA all of the following:
  - All protocols, statistical analytic plans along with any amendments and dates of amendments for all studies that provide major support for the indications sought.
  - Adequate financial disclosure information (see response to the 15 November 2011 meeting minutes to a requested waiver for this information which was not obtained during the course of the ivabradine clinical development program).

- MedDRA coding dictionaries for any AEs of special interest as SAS transport files.
  - A SAS AE dataset that contains the following:
    - Original and final AE terms with date and times of entry,
    - Deleted AE terms with date, time, and reason for deletion,
    - AE sequence number that, with the subject ID, uniquely identifies the AE.
    - If applicable, the CIOMS and/or Medwatch number
    - If the AE is an endpoint, please flag the observation.
  - A table detailing all of the tables and figures featured in the main section of the SHIFT and BEAUTIFUL clinical study reports, and the Summary of Clinical Safety. The table should contain the following:
    - title of the table or figure, location, and hyperlink to the table or figure,
    - SAS code (hyperlink) and dataset (s) used to create the table or figure. Note that if a SAS macro was used within a SAS code, then the macro should also be listed and hyperlinked in the table.
  - Sample clinical trial kits, identical to those used during the trial including both placebo and active drug. Ship them to Alexis Childers' desk address in the same packaging as was used for shipping to investigative sites.
  - A description of the responsibilities of each CRO used in SHIFT.
  - All versions of your clinical trial monitoring plan for SHIFT.
  - All versions of your detailed data management plan, including both manual and programmed data checks used throughout the study as well as those that triggered identification of endpoints for adjudication.
  - A detailed description of how study drug was packaged and maintained at the study sites, as well as how drug was dispensed to subjects. Please indicate if:
    - If kits dedicated in advance to individual subjects?
    - How dispensing and drug return records created and maintained?
- Also, describe in detail your methodology for detecting medication errors during and after the study, monitoring for such errors and any corrective actions taken with regard to medication errors.
2. Attached to these preliminary responses is an information request provided by the Office of Scientific Investigations. This document includes data requests that are to be addressed in your initial submission.
  3. Indicate, including the number of subjects, which sites are currently able to be inspected.
  4. Also attached to these preliminary responses is the Clinical Pharmacology Review Aid. Please refer to this document when putting together clinical pharmacology information in your dossier.

5. The relationship between heart rate lowering and clinical outcomes is of interest and will be investigated by the review team. We recommend that you evaluate this relationship and provide the full report, SAS datasets, and programs as part of the NDA submission.
6. 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. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.
7. We expect you to submit all pharmacology/toxicology studies necessary to support your NDA in a standard format. Please be aware that the tumor data from each carcinogenicity study need to be provided as an electronic analysis dataset as outlined in *Study Data Specifications, Version 2, July 18, 2012*  
<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>
8. In the appropriate sections of the clinical analyses, please address the following:
  - Subgroup analyses to include:
    - study outcomes based on concomitant medications other than beta blockers
    - study outcomes for patients experiencing myocardial ischemia during the trial (the majority of HFrEF patients will have an ischemic substrate)
  - Holter or other long-duration rhythm records to describe the human counterpart, if it exists to the sinus arrest that ivabradine was noted to cause in dogs.
  - A discussion of a correlation, if one exists, of the degree of heart rate reduction and the occurrence of pertinent/rate-related adverse events
  - A discussion of potential drug interactions that could potentiate rate-related QT prolongation or symptomatic bradyarrhythmias
  - A discussion of your rationale for dose selection for testing in SHIFT and BEAUTIFUL
9. Steering Committee and DSMB meeting minutes (including any data/slides presented to the Committee). Please include a place holder for any meeting for which minutes are not available noting why the minutes are not available. Please ensure the minutes for each meeting are included in the table of contents and are bookmarked by date.
10. Per our 15 November 2011 meeting minutes regarding documentation that should be submitted relative to the activities and decisions of your clinical event committee (Question 4 of those minutes), please note that the following descriptions/explanations/data elements are expected with the submission:
  - How possible endpoint events identified at clinical trial sites were handled and sent to the adjudication committee (manual triggers).
  - How possible endpoint events not identified at clinical trial sites were identified and sent to the adjudication committee (automated triggers).

- The number of endpoint events identified at sites and subsequently submitted to the adjudication committee as well as the number identified at sites that subsequently were NOT submitted to the adjudication committee. Please supply reason(s) why endpoints identified by sites but not submitted were not submitted for every such occurrence.
  - How adjudication packets were prepared for and submitted to the adjudication committee. In particular, how blinding was maintained in the preparation and submission of endpoint information to the adjudication committee
  - All records of adjudication committee meetings including charters, presentations, etc.
  - A description of the procedure, charter, definitions used to adjudicate endpoint. How reconciliation was made when different members of the adjudication did not agree
  - How the hospitalization information was databased in your data management system and how blinding was ensured.
  - Outcome of adjudication of “sequence events” – i.e., > 1 endpoints occurring during the same day.
  - Records of any interaction between (a) members of the adjudication committee and data monitoring committee, and (b) members of the adjudication committee and the steering committee.
  - A line listing of all hospitalizations, including those not submitted to the adjudication committee,
  - Whether there were “back adjudication” or “re-adjudication” and how these were processed and reconciled, and
  - Tabulation of individual member’s adjudications to determine inter-reviewer variability and/or potential bias in any member in adjudicating the endpoints.
  - The complete adjudication package that was sent to each adjudicator for each event adjudicated.
  - A data set containing one line per event with unique subject id, the date of the event, the reason for adjudication, each adjudicator’s result and date (in chronological order), and the final adjudication result and date.
11. Your proposed draft Module 1 TOC, is acceptable.
12. In addition, to submit PSUR descriptive portion (only) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Sponsor should ensure that the leaf title of the report includes the reporting period, since each report is for a specific time period and it also helps when the leaf title follows a standard format, so reviewers can quickly differentiate one report from another. The descriptive portion of the Periodic ADE Report in module 5.3.6 should not contain the 3500a forms, but instead, at the end of the summary, it should specify how the 3500a forms were submitted. For example, sponsor would reference the 3500A forms were submitted in Paper to AERS or the 3500A forms were sent in E2B XML format via the Electronic Submissions

Gateway. For Steps to Submitting ICSRs Electronically in the XML Format, please visit: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115914.htm>. If sponsor submits the 3500A forms in paper, It's recommended that sponsor provide the date of the submission, address shipped to, as well as any other pertinent information.

Below is the address for the 3500A paper submissions:

FDA/Central Document Room  
Attn: AERS 3500A Reports Production  
5901-B Ammendale Rd.  
Beltsville, MD. 20705-1266

13. If you are going to cross reference previously submitted documents options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

- To use the first option (placing a cross reference document in m1.4.4), a PDF document would be placed in m1.4.4 (cross reference to other applications) with a description of what is being cross referenced, and where those original documents resides. Hyperlinks to those documents are optional, but could be of help to reviewers, if provided.
- To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g., nda, ind). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf titles allows the reviewer to know that the document resides in another application and what application is being referenced.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov). Please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

From a technical standpoint (not content related) the planned format for Module 1, is acceptable. However, please see additional comments below:-

- Place the Priority Review Request in m1.2 section as a separate document from the cover letter and provide clear leaf title so reviewers can easily identify the document.
- Providing a linked reviewer's aid/ reviewer's guide in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, can be helpful to reviewers.
- 1.6.3 Correspondence regarding meetings: a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
- Case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Do not use 5.3.7 as a heading element in the index.xml. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at:  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

**Discussion during meeting:** The only item discussed under "Additional Comments" during the meeting was item #2 regarding clinical investigator site inspections. The sponsor indicated that in this instance, the pilot program is not the best to comply with. They proposed to supply Part I and Part III with the initial submission, and later submit Part II for only the sites that the Agency has chosen to inspect. The OSI reviewer indicated she will follow up with her team to confirm acceptability.

**POST-MEETING NOTE:** After the meeting the reviewer emailed the sponsor on January 27, 2014 stating that it is acceptable to submit Part I and III with the initial submission but stated that Part II would need to be submitted within 5 business days once we inform them of the sites we plan to inspect. The sponsor confirmed agreement via email on January 27, 2014.

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

- The content of a complete application was discussed. See comments above for discussion and agreements for the clinical Pre-NDA meeting. A separate CMC Pre-NDA meeting was held on December 6, 2013. The content of a complete application was discussed. Refer to those meeting minutes dated December 23, 2013 for specific CMC discussion.

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 REMS was held and it was concluded that a REMS is not needed.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 5 business days after the Agency informs the sponsor of selected sites.  
Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

**NDA NUMBER: LATE COMPONENT - BIOMETRICS**

**NDA NUMBER: LATE COMPONENT - CLINICAL**

**NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY**

**NDA NUMBER: LATE COMPONENT - NONCLINICAL**

**NDA NUMBER: LATE COMPONENT - QUALITY**

### **PREA REQUIREMENTS**

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

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

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

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of 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, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

## **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**

None

**5.0 ACTION ITEMS**

None

**6.0 ATTACHMENTS AND HANDOUTS**

Sponsor slides entitled "FDA Pre-NDA Meeting for Ivabradine".

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

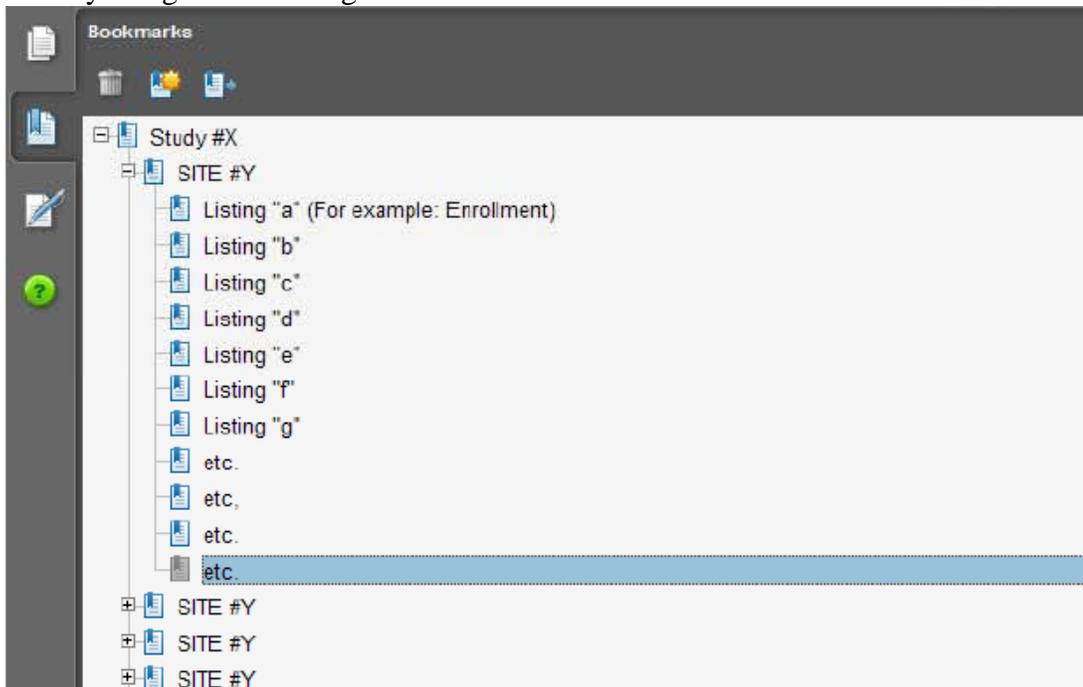
**I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Number of subjects screened for each site by site
  - b. Number of subjects randomized for each site by site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
  - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
  - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



**III. Request for Site Level Dataset:**

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## **Attachment 1**

### **1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions**

#### **1.1 Introduction**

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### **1.2 Description of the Summary level clinical site dataset**

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)**

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

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MINITAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

## Attachment 2

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

OSI Pre-NDA for NDA 206143

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

# CLINICAL PHARMACOLOGY SUMMARY AID

## 1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To better communicate the expectations of the Agency and to guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a Clinical Pharmacology Summary Aid was created. The document consists of a generic questionnaire and instructions clarifying what the answers to the questions should address. The questions cover the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired backbone of the Clinical Pharmacology Summary in NDA and BLA submissions. The questions and instructions included in this aid are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

## 2. Question Based Review

### 2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

### 2.2 General Attributes of the Drug

#### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics

(Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

**2.2.3 What are the proposed dosages and routes of administration?**

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

**2.3 General Clinical Pharmacology**

**2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

**2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

**2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

## **2.4 Exposure-Response**

### **2.4.1 Does the exposure-response relationship support evidence of effectiveness?**

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from pivotal and other appropriate trials. Provide evidence that the exposure-response analysis supports of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If commonly known covariates are not identifiable, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for effectiveness variables if applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

### **2.4.2 What are the characteristics of the exposure-response relationships for safety?**

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal

status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C<sub>max</sub> and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

### **2.4.3 Does this drug prolong QT/QTc Interval?**

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

### **2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the pivotal trials. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

## **2.5 What are the PK characteristics of the drug?**

### **2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C<sub>max</sub>, t<sub>max</sub>, AUC, C<sub>max,ss</sub>, C<sub>min,ss</sub>, C<sub>max,ss</sub>/C<sub>min,ss</sub>, t<sub>max,ss</sub>, AUC<sub>0-τ</sub>, CL/F, V/F and t<sub>1/2</sub> (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

**2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

**2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C<sub>max</sub>, C<sub>min</sub>, CL/F and t<sub>1/2</sub> of the parent drug and relevant metabolites after single doses and at steady-state.

**2.5.4 What are the characteristics of drug absorption?**

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, t<sub>max</sub>, t<sub>max,ss</sub>, C<sub>max</sub>, C<sub>max,ss</sub> and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

**2.5.5 What are the characteristics of drug distribution?**

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

**2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

**2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**

Provide identification for  $\geq 90\%$  of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small

to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

#### **2.5.8 What are the characteristics of drug metabolism?**

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

#### **2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?**

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

#### **2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?**

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

#### **2.5.11 What are the characteristics of drug excretion in urine?**

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

#### **2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C<sub>max</sub> and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

### **2.5.13 How do the PK parameters change with time following chronic dosing?**

Indicate whether the mean ratio of AUC<sub>0-τ</sub> at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

### **2.5.14 Is there evidence for a circadian rhythm of the PK?**

Indicate whether C<sub>max</sub> and C<sub>min</sub> of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

## **2.6 Intrinsic Factors**

### **2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C<sub>max</sub>, clearance, volume of distribution and t<sub>1/2</sub> for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

### **2.6.2 Based upon what is known about E-R relationships in the target**

## **population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

### **2.6.2.1 Severity of Disease State**

### **2.6.2.2 Sex**

### **2.6.2.3 Body Weight**

### **2.6.2.4 Elderly**

### **2.6.2.5 Pediatric Patients**

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

### **2.6.2.6 Race/Ethnicity**

### **2.6.2.7 Renal Impairment**

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C<sub>max</sub>, CL/F, CL<sub>r</sub>, V/F and t<sub>1/2</sub> of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C<sub>max</sub> and CL/F on CL<sub>r</sub> for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the

sub-groups of patients with impaired renal function and provide a rationale for either scenario.

#### **2.6.2.8 Hepatic Impairment**

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C<sub>max</sub>, CL/F and t<sub>1/2</sub> of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C<sub>max</sub>, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

#### **2.6.2.9 What pregnancy and lactation use information is available?**

#### **2.6.3 Does genetic variation impact exposure and/or response?**

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

#### **2.6.4 Immunogenicity (NOT applicable to small molecule drugs)**

##### **2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

**2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

**2.6.4.3 Do the anti-product antibodies have neutralizing activity?**

**2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?**

**2.6.4.5 What is the impact of anti-product antibodies on clinical safety?**

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

## **2.7 Extrinsic Factors**

**2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

**2.7.2 Is the drug a substrate of CYP enzymes?**

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to  $K_m$ , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

**2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?**

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for  $K_i$ ,  $IC_{50}$  and  $V_{max}$  for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as

inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/K<sub>i</sub> ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

**2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

**2.7.5 Are there other metabolic/transporter pathways that may be important?**

**2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

**2.7.7 What are the drug-drug interactions?**

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the

magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> of each of the co-administered drugs in the presence and absence of the drug of interest.

- 2.7.8 Does the label specify co-administration of another drug?**
- 2.7.9 What other co-medications are likely to be administered to the target population?**
- 2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

## **2.8 General Biopharmaceutics**

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C<sub>max</sub> after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

### **IR Product**

- 2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?**
  - 2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**
  - 2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**
- 2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Indicate composition and calories of the food administered, and length of the

pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

- 2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?**
- 2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

**MR product (if an IR is already marketed)**

- 2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?**

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C<sub>max</sub>, AUC and C<sub>min</sub> of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

- 2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?**
- 2.8.8 What is evidence that MR formulation displays less variability in C<sub>max</sub>, AUC and C<sub>min</sub> than IR formulation?**
- 2.8.9 Does the MR product show dose dumping *in vivo*?**

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

- 2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?**

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

**2.8.11 Are the MR and IR products marketed simultaneously?**

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

**2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?**

**2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?**

**2.9 Analytical Section**

**2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?**

List all assays used and briefly describe the individual methods.

**2.9.2 Which metabolites have been selected for analysis and why?**

**2.9.3 For all moieties measured, is free, bound, or total measured?**

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

**2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?**

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

**2.8.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?**

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic

regimens. Indicate fit type of the calibration curves.

**2.9.5.1 What are the lower and upper limits of quantitation?**

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

**2.9.5.2 What are the accuracy, precision, and selectivity at these limits?**

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

**2.9.5.3 What is the sample stability under conditions used in the study?**

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at  $\leq -20^{\circ}\text{C}$ .

**2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?**

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

**Applicable to therapeutic proteins only**

**2.9.5.5 What bioanalytical methods are used to assess therapeutic protein concentrations?**

Briefly describe the methods and summarize the assay performance.

**2.9.5.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies?**

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

**2.9.5.7 What is the performance of the neutralizing assay(s)?**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NORMAN L STOCKBRIDGE  
02/18/2014



NDA 206143

**MEETING MINUTES**

Amgen Inc.  
Attention: Geza Ekecs, Sr. Manager  
Regulatory Affairs, CMC  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Ekecs:

Please refer to your New Drug Application (NDA) dated September 26, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ivabradine, Tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 6, 2013. The purpose of the meeting was to discuss the proposed data package that will be presented in the NDA to support the registration of ivabradine.

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

If you have any questions, call 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 Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA/CMC Only

**Meeting Date and Time:** Friday December 6, 2013, 10:00 AM -11AM (EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1419  
Silver Spring, Maryland 20903

**Application Number:** NDA 206143  
**Product Name:** Ivabradine  
**Indication:** Treatment of chronic Heart Failure (b) (4)

**Sponsor/Applicant Name:** Amgen Inc.

**Meeting Chair:** Olen Stephens, Ph.D.  
**Meeting Recorder:** Yvonne Knight, MS, RPM

### FDA ATTENDEES

Olen Stephens, Ph.D., CMC Acting Branch Chief  
Pei-I Chu, Ph.D., Product Quality Reviewer  
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader  
Yvonne Knight, Regulatory Project Manager

### SPONSOR ATTENDEES

Geza Ekecs, Senior Manager, Regulatory Affairs CMC, ivabradine  
Tegan Wheeler, Senior Associate, Regulatory Affairs CMC, ivabradine  
Ben Zhi, Ph.D., Product Quality Director  
Shawn Walker, Ph.D., Principal Scientist, Chemical Process R&D  
Paco Alvarez, Ph.D., Director Process Development  
Kirby Wong-Moon, Ph.D., Principal Scientist, Analytical R&D  
Marc Lujan, Executive Director Global Operations  
Rameshraj Palaparthi, Ph.D., Principal Scientist, Pharmacokinetics  
Brandon Swift, Ph.D., Senior Scientist, Pharmacokinetics  
Christine Kubik, Senior Manager, Regulatory Affairs, ivabradine

(b) (4)



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

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## **1.0 BACKGROUND**

Reference is made to NDA 206143 for ivabradine. The sponsor submitted a type B meeting request on September 26, 2013. The purpose of this meeting was to review the chemistry, manufacturing and controls data currently available to support an NDA for ivabradine for chronic Heart Failure (HF) indication. The meeting request was granted on October 16, 2013. Background packages were received on November 4, 2013. Preliminary Responses were sent to the sponsor on November 27, 2013. The sponsor provided responses to the Agency's comments on December 5, 2013.

The following outcomes were expected from the meeting:

1. Confirm that the proposed drug product manufacturing site change does not require a bioequivalence study and Amgen can submit a biowaiver.
2. Reach agreement on the adequacy of the proposed drug substance and drug product release strategy.
3. Obtain agreement that the stability data packages planned for filing in the NDA will support the proposed expiry dating for the drug product in blisters and bottles.
4. Confirm and reach agreement on the proposed starting material and manufacturing synthesis strategy.

## **2.0 DISCUSSION**

***Question 1:*** *Preclinical, clinical and analytical data confirm that ivabradine is highly soluble, highly permeable, well absorbed, and dose linear in its exposure and has an acceptable therapeutic index. Although the drug product manufacturing site will change, given these drug characteristics, no changes in qualitative and quantitative composition of the drug product, and minimal process changes, Amgen does not believe a human bioequivalence study is necessary and plans to submit a biowaiver. Does the Agency agree?*

### **FDA Response to Question 1:**

#### ***From CMC Perspective:***

Yes, we agree. You will still need to provide information on the equipment and process used to demonstrate that the products are of the same quality and meet the same specification. The adequacy of the data provided will be evaluated during the NDA stage.

***Biopharmaceutics Response:***

- 1) As per SUPAC-IR, the manufacturing site changes with minor process changes you plan to implement to your immediate release drug product correspond to a Level 3 site change requiring multipoint dissolution profile comparisons in the regulatory dissolution method and do not require BE documentation. Therefore, a biowaiver is not applicable.
- 2) Include an appropriate statistical analysis (e.g.  $f_2$  testing, if appropriate) supporting the profiles similarity.
- 3) Note that if the changes are major and you are planning on using (b) (4) designation to waive the BE requirements, you need to submit the data supporting the (b) (4) claim as an amendment to the IND. Note that it takes 2-4 months for the review of these data. Your amendment should clearly state its purpose and should include the data listed under additional biopharmaceutics comments to facilitate the review.

**Sponsor's Pre-Meeting Response:**

- Amgen acknowledges the Agency's feedback.
  - Ivabradine drug product site, equipment, and process changes are minor, and data will be provided with the NDA.
  - A biowaiver is not applicable for ivabradine.
- Dissolution for current and proposed manufacturing sites show (b) (4) release ( $>$  (b) (4) % in 15 minutes, therefore,  $f_2$  is not applicable).
- With agreement that these are minor changes, we would like to confirm that a bioequivalence study is not required.

***Meeting Discussion: Amgen acknowledged that the manufacturing processes were the same with minor changes. The Agency agreed that if the changes were minor, the Bioequivalence study is not required and therefore a Biowaiver is not applicable.***

**Question 2:** *Does the Agency agree that the proposed drug substance and drug product specification strategies are appropriate for ivabradine commercial registration?*

**FDA Response to Question 2:**

***From CMC Perspective:***

Agreement on specifications and their limits will occur at the time of NDA review. With that said, we have the following observations and comments.

- 1) Include a test for (b) (4) in the drug substance specification since (b) (4) was used during synthesis.

- 2) Skip-lot testing for drug products is not allowed by regulation (21 CFR 211.165 (a) and (b)) for microbial testing; therefore, include microbial limits testing on all batches or provide adequate justification to demonstrate this attribute test is not necessary. Microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process will be needed. Address the following points in your NDA submission:
  - a) Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. For example:
    - i. Define the maximum processing time for the (b) (4) step.
    - ii. Define the maximum holding time for the coating solution.
  - b) Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
  - c) Describe activities taken when microbiological acceptance criteria are not met at control points.
  - d) Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. If you remove microbial limits testing from the release specification, then you should perform microbial limits testing at the initial testing time point as part of your stability protocol. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

- 3) Particle size testing may be omitted from the drug substance release specification if adequate justification and data are provided to demonstrate that the particle size distribution of the drug substance will not affect the manufacturability and physical chemical property of the drug product. If it is determined that particle size analysis is needed, skip-lot testing would not be acceptable and it should be performed on every batch for release and stability testing. Furthermore, depending on your data, acceptance criteria for particle size distribution may need to be reported as a distribution (i.e. Dv10, Dv50, and Dv90) instead of simply reporting Dv50.
- 4) We have noticed that the established test limits for shelf-life determination and release are not the same (see question#3). Note that there is only one set of regulatory specifications in an NDA. Your drug product must meet this set of specifications throughout the claimed product shelf life. However, it is permissible that you maintain an internal set of release specifications. In your application, this internal set of release specifications can be discussed

as part of your overall control strategy. When you submit your NDA, align the drug product specifications to the end of shelf-life specifications and classify the release specifications as an internal set of specifications part of your overall control strategy.

5) Refer also to the comment below in response 4 regarding [REDACTED] (b) (4).

***Biopharmaceutics Response:***

It is noted that dissolution is not included as part of the drug product specifications. Clarify if it is your intention to use disintegration testing in lieu of dissolution. If that is the case you need to submit the following/justification information:

- 1) Your proposed product contains a drug which is [REDACTED] (b) (4) soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to [REDACTED] (b) (4)).
- 2) Your proposed drug product is [REDACTED] (b) (4) dissolving (dissolution [REDACTED] (b) (4) % in 15 minutes at pH [REDACTED] (b) (4)).
- 3) Disintegration is shown to be more discriminating than dissolution towards relevant material attributes and manufacturing variables.

**Sponsor's Pre-Meeting Response:**

- Amgen agrees to add a drug substance release specification for [REDACTED] (b) (4).
- Microbial Limits will be tested for every drug product lot. [REDACTED] (b) (4).
- Amgen acknowledges the Agency's comments on the option to omit particle size testing from the specification for the drug substance if properly justified.
- We believe that removal of particle size testing can be justified given:  
[REDACTED] (b) (4)
- Amgen agrees to provide a single specification for release and shelf life.
- Amgen agrees to provide the control strategy for [REDACTED] (b) (4).
- Amgen agrees to justify using disintegration instead of dissolution per ICH Q6A.
  - However, Amgen would like to verify that the dissolution data at 0.1 N HCl, pH 4.5 and pH 6.8 provided in the briefing document is acceptable as per FDA Guidance\*.

\*Guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*

**Meeting Discussion:** Amgen agreed to test for (b) (4) in drug substance and to test microbial limits for every drug product lot.

**The Agency reaffirmed that an adequate justification in the context of a well-controlled manufacturing process must be demonstrated before particle size testing can be omitted from the specification. Historical data should be provided in the NDA to support any justification to omit the particle size specification.**

**The Agency confirmed that the proposed media (0.1 N HCl, pH 4.5 and pH 6.8) for use in the dissolution studies are acceptable. Data for both dissolution and disintegration should be provided in the NDA for the registration batches.**

**Question 3:** *At the time of the NDA submission, the dossier will include:*

- 36 months of real-time data for drug substance
- 36 months of real-time data for drug product in blisters from two (b) (4) commercial manufacturing sites
- 3 months of real-time data for drug product in blisters from (b) (4) the proposed commercial manufacturing site
- 3 months of real-time data for drug product in bottles from (b) (4), the proposed commercial manufacturing site

*The drug product composition of the 5 mg and 7.5 mg tablets and blister configurations used are the same at all three drug product manufacturing sites.*

*Does the Agency agree the proposed drug substance and drug product (blisters and bottles) stability package described above is adequate to support a (b) (4) re-test date for ivabradine drug substance and a 3-year expiry date for ivabradine blisters and bottles for commercial registration?*

*Does the Agency also agree that Amgen may amend stability data from the proposed commercial manufacturing site during review of the NDA?*

### **FDA Response to Question 3**

**From CMC Perspective:**

In order to bridge the stability data from the two sites, we will first need to review the information you provide on the equipment and process used for the commercial batches and your ability to demonstrate that the products are of the same quality. The ability to bridge the stability data from the (b) (4) and (b) (4) manufacturing sites will determine the shelf life supported by your stability data. In addition to the stability data obtained from batches manufactured at (b) (4), you should file your NDA with release data of the three batches made at the commercial site ( (b) (4) ) and 3 months of stability data from these batches stored under long-term and accelerated conditions. After the initial three commercial batches, one batch per year should be placed on stability. The adequacy of the data will be evaluated during the NDA stage.

After filing the NDA, stability data updates may be submitted to the NDA as amendments and they will be reviewed as resources allow.

***Meeting Discussion: Amgen confirmed that three months of accelerated stability data will be included in the NDA in addition to the stability package presented in the meeting package.***

***Question 4:*** Does the Agency agree on the designation of the proposed starting materials in the manufacturing synthesis strategy?

**FDA Response to Question 4:**

***From CMC Perspective:***

No, we do not agree with your proposed starting materials (b) (4) (b) (4) are more appropriate starting materials because (b) (4) process under cGMP control. When you submit your NDA, you should provide data or a rationale to demonstrate how changes in the manufacturing process of starting materials will affect the impurity profile of the drug substance.

In addition, we note that the (b) (4) is formed using (b) (4) which is a potential genotoxic impurity. Measure the (b) (4) in (b) (4) or in the drug substance and demonstrate that it does not exceed the TTC level. Alternatively, genotoxicity tests using the purified impurities can be conducted. If they are negative, this impurity would only require assessment if their levels exceed the threshold for qualification.

**Sponsor's Pre-Meeting Response:**

- Amgen acknowledges the FDA comments regarding the suitability of (b) (4) (b) (4) as starting materials.

- Amgen believes there is compelling data demonstrating that (b) (4) are appropriate starting materials, and would like to further discuss the starting material designation.
- Extensive commercial manufacturing history is available, (b) (4)
- None of the impurities listed in the drug substance specification are derived from impurities from (b) (4).
- (b) (4)
- (b) (4)

Considering the data presented, what additional data can be presented to approve (b) (4) as designated starting materials?

***Meeting Discussion:*** The sponsor agreed to designate (b) (4) as a starting material. The Agency reiterated that (b) (4) would not be an acceptable starting material, (b) (4). The Agency referred the sponsor to the ICH Q11 Guidance for principles used to select a drug substance starting material: “Development and Manufacture of Drug Substances,” available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf>

***Additional Biopharmaceutics Comments:***

- 1) ***Dissolution Test:*** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
  - a) Solubility data for the drug substance covering the pH range;
  - b) Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no*

increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

- c) Provide the complete dissolution profile data (*individual, mean, SD, profiles*) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
- d) Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e.,  $\pm 10\text{-}20\%$  change to the specification-ranges of these variables) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.) In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

**2) Dissolution Acceptance Criteria:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

- a) The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).
- b) Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
- c) A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least 80% of drug has release. If the maximum amount release is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.

3) The following data supporting the (b) (4) should be submitted as an amendment to the IND for review:

**A. INFORMATION NEEDED TO SUPPORT A (b) (4) DRUG SUBSTANCE**

**1. Determination of Drug Substance Solubility Class**

- 1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance?
- 1.2 What is the nature of the drug substance (acid, base, amphoteric, or neutral)? What is the dissociation constant(s), PKa(s) of the drug substance?
- 1.3 What is the solubility profile of the drug substance under physiological pH conditions (i.e., pH range (b) (4) at 37°C in aqueous media)?
- 1.4 Were five pH conditions used to define the solubility pH profile? How many replicate determinations of solubility of the drug substance at each pH condition were performed?
- 1.5 What type of buffer solutions were used to define the solubility profile? What are the compositions of the buffer solutions? How they were prepared?
- 1.6 Was the buffer solution's pH verified after the addition of the drug substance to the buffer?
- 1.7 What type of method was selected to evaluate the equilibrium solubility of the drug substance? What are the specific experimental testing conditions?
- 1.8 What analytical method was used to determine the concentration of the drug substance in the selected buffers (or pH conditions)? What data support the validation of the assay?
- 1.9 What are the solubility pH profile results (individual, mean, standard deviation, coefficient of variation, and graphics)?
- 1.10 Is the highest dose strength of the proposed drug-product soluble in 250 ml of aqueous media over the pH range of 1 to 7.5?
- 1.11 Is the overall solubility information supportive of a (b) (4) classification for the drug substance?

**2. Determination of Drug Substance Permeability Class**

- 2.1 What approach was used to determine the permeability class of the drug substance (i.e., *in vivo mass balance or absolute BA or intestinal permeability*)? If more than one method was used to demonstrate permeability classification, what is the other(s) approach?

- 2.2 For human pharmacokinetic approaches - Which approach was selected (*i.e., mass balance and/or absolute BA*)? What is the information describing the study design, methods, results, etc?
- 2.3 For the intestinal permeability approaches – Which method was selected (*i.e., 1) in vivo intestinal perfusion studies in humans; 2) in vivo or in situ intestinal perfusion studies using suitable animal models; 3) in vitro permeation studies using excised human or animal intestinal tissues; or 4) in vitro permeation studies across a monolayer of cultured epithelial cells*) and what is the rationale for its selection?
- 2.4 Is the drug substance being testing a passively transported drug? What is the information supporting this assumption?
- 2.5 Was the linear relationship between the dose and measures of bioavailability (*humans*) demonstrated?
- 2.6 Was there a lack of dependency of the measured in vitro permeability of the test article on initial drug concentration or transport direction (*no difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction*) using a suitable in vitro cell culture method. What is the supportive information?
- 2.7 For the in vivo-human perfusion studies, in vivo or in situ-animal intestinal perfusion studies or in vitro cell culture methods, how many model drugs were used? What model drugs were selected and did they represent a range of absorption values? What are the permeability values for each model drug (mean, SD, CV) and what is the permeability class of each model drug?
- 2.8 What information supports the suitability of the selected method (*i.e., description of the study, criteria for the selected approach, analytical method, method used to estimate the extent of absorption, (where appropriate, efflux potential), results (individual, mean, SD, coefficient of variation), etc.*)? Were the results tabulated? Was the suitability of the selected permeability method(s) adequately demonstrated?
- 2.9 What drugs were selected as low and high permeability internal standards? What is the high permeability internal standard used for the permeability classification?
- 2.10 What is the information supporting the high permeability of the drug substance (*i.e., permeability methods permeability data on the test drug substance and internal standards (mean, SD, & CV), data supporting classification and passive transport mechanism*)?
- 2.11 What is the graphic representation of the extent of absorption as a function of permeability (*mean  $\pm$ SD or 95% CI*) with low/high permeability class boundary and selected internal standard(s). What is the rank-order relationship between test permeability values and the extent of drug absorption values?

2.12 Is the overall information supporting a (b) (4) classification for the drug substance?

### **3. Gastric Stability**

3.1 What is the information supporting the stability of the drug substance/drug product in the GI tract?

3.2 What are the experimental conditions used during the gastric stability experiments?

3.3 Were simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) used to generate the chemical stability data or human fluid? What are the compositions of the SGF and SIF solutions?

3.4 What is the validation information for the analytical method? What is a validated stability-indicating assay?

3.5 What are the SGF and SIF stability results (mean, SD, CV)? Are the results tabulated?

3.6 Is the overall information supportive of gastric stability?

## **B. INFORMATION TO SUPPORT A (b) (4) – DRUG PRODUCT**

The complete information addressing the following questions should be provided to support a (b) (4) classification request for a drug product.

**1. Determination of the Drug Substance Solubility Class (same as A.1).**

**2. Determination of the Drug Substance Permeability Class (same as A.2).**

**3. Determination of the Dissolution Characteristics of the Drug Product**

3.1 What is the information describing the drug product used for dissolution testing (i.e., batch/lot No., expiry date, lot size, strength, etc.)?

3.2 What are the selected dissolution testing conditions (i.e., apparatus, rotation speed, dissolution media, temperature, and volume)?

3.3 What is the sampling schedule? Does the sampling schedule adequately characterize the complete dissolution profile? Were twelve dosage units per experiment tested?

- 3.4 What is the information supporting the validation of the dissolution methodology (robustness, etc.).
- 3.5 What is the analytical method(s) used to determine the concentration of the drug in the dissolution samples? What is the validation information for the analytical method? Was it a validated assay?
- 3.6 Was the dissolution of the drug product characterized in three different pH media? What are the compositions of the buffer solutions? How they were prepared? What are the dissolution characteristics in these media?
- 3.7 What are the dissolution results (*i.e., individual, mean, SD, CV, and graphics*) in the different media? Are the results tabulated? Are the dissolution profile data reported in percent of label claim?
- 3.8 Is the drug product showing fast dissolution in the different pH media? Is more than 85% of drug being dissolved in 15-30 minutes in each medium?
- 3.9 Does the overall dissolution data support a rapid/fast dissolving designation for the drug product?

#### **C. DATA SUPPORTING A REQUEST FOR ANY FUTURE REQUEST FOR BIOWAIVER(s)**

Sponsor requesting a biowaiver(s) for a drug products based on the BCS should submit complete information addressing the following questions.

- 1. Data Supporting [REDACTED] <sup>(b) (4)</sup> for the Drug Substance (same as A.1).**
- 2. Data Supporting [REDACTED] <sup>(b) (4)</sup> for the Drug Substance (same as A.2).**
- 3. Data Supporting Gastric Stability (same as A.3).**
- 4. Data Supporting [REDACTED] <sup>(b) (4)</sup> for the Drug Product (same as B.3).**
- 5. Data Supporting Similar Dissolution for the Test and Reference Products**

- 5.1 What is the information describing the test and reference products used for dissolution testing (*i.e., batch/ lot No., expiry date, lot size, dimensions, strength, weight, etc.*)?

- 5.2 What are the methodology and conditions used for the dissolution testing of the test and reference products? Does the sampling schedule include adequate frequency and sampling times to characterize the complete dissolution profile?
- 5.3 Were the dissolution profiles of the drug product and reference product characterized in different pH media? What are those media and how they were prepared?
- 5.4 What are the dissolution testing results (*individual, mean, range, SD, coefficient of variation*) for the test and reference products in the different dissolution media? Are the dissolution profile comparison data at each tested interval reported in percent of label claim? Was the overall dissolution data tabulated?
- 5.5 What is the graphic representation of the mean dissolution profiles for the test and reference products in the different dissolution media?
- 5.6 Was the similarity f2 metric for the dissolution profiles of the test and reference products estimated? What are the similarity f2 values for each tested media?
- 5.7 Are the overall dissolution profile comparison data and f2 values supporting the biowaiver(s) request?

## 5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide meeting minutes	FDA	January 5, 2013

## 6.0 ATTACHMENTS AND HANDOUTS

Amgen Inc. slides are attached.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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OLEN M STEPHENS  
12/23/2013



pNDA 206143

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Amgen Inc.  
9201 Corporate Boulevard  
Suite 400  
Rockville, MD 20850

ATTENTION: Christine Kubik  
Senior Manager, Regulatory Affairs

Dear Ms. Kubik:

Please refer to your Pre New Drug Application (pNDA) file for Ivabradine.

We acknowledge receipt of your October 2, 2013, correspondence, on October 3, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name Corlanor. This proposed proprietary name request is considered withdrawn as of October 3, 2013.

If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted once the NDA is submitted. (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, call Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Alexis Childers, the Office of New Drugs (OND) Regulatory Project Manager, at (301) 796-0442

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN E BENGTON  
10/22/2013

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



NDA 206143

**LATE-CYCLE MEETING MINUTES**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) dated June 27, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ivabradine, 5 and 7.5 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on 10 December 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 Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Late Cycle Meeting Minutes and presentation



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

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** December 10, 2014 1:30-3:00 pm

**Meeting Location:** White Oak Bldg 22, room 1311

**Application Number:** 206143

**Product Name:** Ivabradine

**Indication:** to reduce the risk of (b) (4) hospitalizations for worsening heart failure (HF) (b) (4) in sinus rhythm with heart rate  $\geq$  70 beats per minute (bpm), (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4) (b) (4)

**Sponsor/Applicant Name:** Amgen, Inc.

**Meeting Chair:** Thomas Marciniak, MD

**Meeting Recorder:** Alexis Childers, RAC

**FDA ATTENDEES**

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

Ellis Unger, MD Director

Robert Temple, MD Deputy Director

*\* Division of Cardiovascular & Renal Products*

Norman Stockbridge, MD, PhD Director

Stephen Grant, MD Deputy Director

Mary Ross Southworth, PharmD Safety Deputy Director

Thomas Marciniak, MD, Cross-Discipline Team Leader (CDTL)

Preston Dunnmon, MD Clinical Reviewer

Nhi Beasley, PharmD Clinical Reviewer

Albert DeFelice, PhD Team Leader, Pharmacology/Toxicology

Jean Wu, Ph.D. Pharmacology/Toxicology Reviewer

Mike Monteleone, MS Associate Director Labeling

Alexis Childers, RAC Sr. Regulatory Project Manager

*\* Office of Clinical Pharmacology*

Rajnikanth Madabushi, PhD Team Leader

Martina Sahre, PhD Reviewer

Jeff Florian, PhD Acting Team Leader – Pharmacometrics

*\* Office of Biostatistics*

Steve Bai, Ph.D. Statistician

*\* Office of New Drug Quality Assessment*

Wendy Wilson, PhD Reviewer

*\* Office of Surveillance and Epidemiology*

Alice Tu	DMEPA Team Leader
Janine Stewart	DMEPA reviewer
Kimberly Lehrfield, PharmD	Team Leader, DRISK
Danny Gonzalez, PharmD, M.S.	Risk Management Analyst, DRISK
Oanh Dang, Pharm D, BCPS	Safety Evaluator
Margie Goulding, Ph.D.	Epidemiology Team Leader
Carolyn Tabak	Safety Evaluator Team Leader

*\* Office of Medical Policy, Division of Medical Policy Initiatives*

Barbara Fuller, RN, MSN, CWOCN	Patient Labeling, Team Leader
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*\* Office of Executive Programs, Division of Advisory Committee & Consultant Management*

Yvette Waples	Team Leader
Kristina Toliver, PharmD	Acting Designated Federal Officer, CRDAC

**EASTERN RESEARCH GROUP ATTENDEES**

Patrick Zhou	Independent Assessor
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**APPLICANT ATTENDEES**

Elliott Levy, MD	Senior Vice President, Global Development
Mark Taisey	Vice President, Regulatory Affairs
Mary Ellen Cosenza, PhD, DABT, RAC	Executive Director, North America Regulatory Affairs
Lisa Mathis-Bollinger, MD, FAAP	Executive Director, Global Regulatory Affairs
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Christophe Depre, MD	Medical Director, Clinical Research
Dominique Bertin-Millet, MD	Executive Medical Director, Global Safety
Mariano Janiszewski, MD, PhD, MBA	Senior Medical Scientist, Global Safety
Arline Nakanishi, MS	Executive Director, Biostatistics
Chao-Yin Chen, PhD	Senior Manager, Biostatistics
Hugo Vargas, PhD, DABT	Scientific Director, Toxicological Sciences
Rameshraj Palaparthi, PhD	Principal Scientist, Quantitative Pharmacology, Pharmacokinetics and Drug Metabolism

**1.0 BACKGROUND**

NDA 206143 was submitted on 27 June 2014 for Ivabradine, 5 and 7.5 mg tablets.

Proposed indication: to reduce the risk of (b) (4) hospitalizations for worsening heart failure (HF) (b) (4) in sinus rhythm with heart rate  $\geq 70$  beats per minute (bpm). (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4).

PDUFA goal date: 27 February 2015

FDA issued a Background Package in preparation for this meeting on 2 December 2014.

## 2.0 DISCUSSION

### 1. Introductory Comments

**Discussion during meeting:** After introductory comments, Dr. Marciniak informed Amgen that the Advisory Committee meeting scheduled for January 14, 2015 will be postponed, and the review clock will be extended 3 months. He stated that issues are complex and it was determined that SIGNIFY data needs to be reviewed in detail.

Dr. Unger further explained that the Division declared a major amendment as this is potentially a major drug for a major problem; therefore, we want to ensure the review is done thoroughly. He emphasized that senior management has not reviewed the application, but the understanding thus far are that the issues relate to populations for approval and not approvability.

### 2. Discussion of Substantive Review Issues

#### **Clinical:**

- **Trial inconsistencies.** The inconsistencies among the three Phase 3 trials are concerning. In SHIFT the major benefit of ivabradine was a reduction in heart failure (HF) hospitalizations while results for MI were neutral. In BEAUTIFUL HF hospitalization results were neutral while there appeared to be a benefit for MI. The latter results inspired SIGNIFY, but SIGNIFY failed to confirm a benefit and suggests a detrimental effect in patients with symptomatic angina. We need to understand the reasons for these disparate trial results in order to confirm that there is a benefit in heart failure, and to identify particular subgroups for which benefit may be less.

**Discussion during meeting:** Dr. Marciniak stated that the results of the trials are not being disputed as a whole but there are questions since the three trials showed inconsistencies (see attached slides for detailed description of discussion points). SHIFT showed a decrease in heart failure hospitalization and minimal if any decrease in CV death. BEAUTIFUL was neutral for CV death and heart failure hospitalization, but there appears to be a benefit for MI. In SIGNIFY results are neutral for CV death and MI in symptomatic angina patients and there is harm in ischemic heart disease patients. Dr. Marciniak feels that loop diuretic use, heart rate, ischemic etiology and beta blocker usage may be factors in explaining the inconsistencies.

Amgen believes that the trials are consistent and emphasized that the trials cannot fully be compared. They stated that SHIFT was designed specifically to test ivabradine in symptomatic heart failure whereas the other two trials enrolled stable ischemic heart disease. Patients in BEAUTIFUL that would have qualified for SHIFT do show a benefit in *post hoc* analysis. Amgen emphasized that subjects in SHIFT were much sicker than patients in BEAUTIFUL (symptomatic CHF with an LVEF  $\leq$  35% and a hospitalization for HFrEF in the preceding 12 months, as opposed to stable CAD with or without stable CHF) and demonstrated a higher exposure-corrected event rate. Patients in SHIFT were

required to have higher resting heart rates (70 versus 60 bpm), an important difference for a use/rate dependent membrane-active rate-slowing agent. The lower dose of ivabradine was not tested in BEAUTIFUL, and the mean achieved heart rate in BEAUTIFUL was lower in than in SHIFT. SIGNIFY patients differed even more, with preserved LV systolic function at baseline as a group, no important heart failure symptomatology, and no antecedent hospitalization for worsening heart failure in the 12 months before screening. In addition, a higher dose range was tested in SIGNIFY. In all, these elements combined to support the sponsor's hypothesis that SHIFT enrolled a very different group of patients than did BEAUTIFUL and SIGNIFY, and tested a different dosing algorithm.

- Loop diuretic interaction. As communicated by Dr. Marciniak on October 6, 2014 during the midcycle communication meeting, the most consistent finding among the three trials is a favorable interaction between ivabradine and loop diuretic use. The interaction is highly statistically significant in SHIFT and suggests a CV mortality benefit of ivabradine in the ischemic patients on a loop diuretic (and suggests a benefit in the non-ischemic patients regardless of loop diuretic use.) In BEAUTIFUL there is a marginally significant interaction for CV mortality, but the effect ranges from no difference with baseline loop diuretic use to a detriment without it. In SIGNIFY there is the suggestion of an interaction for definite CV mortality (excluding unknown deaths) that is significant if post-randomization loop diuretic use is analyzed. A mechanistic explanation of why there is a CV mortality benefit with the interaction in SHIFT whereas there are, at best, neutral results in BEAUTIFUL and SIGNIFY would be helpful. Regardless, the loop diuretic interaction does not explain the differences in HF hospitalizations between the three studies: highly beneficial with ivabradine in SHIFT, neutral in BEAUTIFUL, and leaning negatively in SIGNIFY.

**Discussion during meeting:** Dr. Marciniak stated that loop diuretic use at baseline was high in SHIFT, intermediate in BEAUTIFUL and low in SIGNIFY. He explained that patients not on a loop diuretic had a pronounced risk of CV death. He believes there is a benefit for patients on both a loop diuretic and ivabradine. If loop diuretics are the best discrimination as to who gets benefit from ivabradine, then Dr. Marciniak feels it should be so stated in the label.

In response to Dr. Marciniak's analyses and statements (see attached), Amgen stated:

- The volume status of HFrEF patients can be dynamic - loop diuretics are started and stopped based on the patient's overall volume status. Accordingly, having a label-driven fluctuation in the use of or dosing of ivabradine based on diuretic use and/or dosing would not be either achievable or appropriate. Amgen further pointed out that Dr. Marciniak's analysis suggesting a relationship between loop diuretics and CV outcomes is flawed because:
  - There is a lack of biological plausibility that ivabradine has a direct interaction with loop diuretics.
  - This putative interaction is based on a retrospective, unblinded, unrandomized, mathematical manipulation of the SHIFT data that did not control for multiplicity.

- This analysis is virtually certain to be confounded by differences in severity of illness (i.e., severe LV dysfunction and symptomatic heart failure in SHIFT resulting in higher adrenergic drive, higher baseline heart rates, higher exposure-adjusted event rates, and thus a measurably positive response to a membrane-active rate slowing medication like ivabradine, especially in those that could not tolerate beta blockers for non-rate-related reasons).

Dr. Marciniak explained that he also looked at heart rate. He noted that there appears to be more of a benefit of ivabradine at higher heart rates, but it could be confounded by beta blocker (BB) usage. Patients were supposed to be on maximum tolerated doses of BB, or intolerant of any dose. Dr. Marciniak explained that the CV mortality benefit decreases as the BB dose increases, but the HF hospitalization is not dependent on BB usage. He also stated the difference seen is in ischemic vs. nonischemic patients.

Amgen found this argument difficult to understand, given that their analysis showed no important differences in the responses of patients with ischemic versus non-ischemic HFrEF. Although Amgen agrees that it is important to do exploratory analyses, they feel that exploratory analyses should be interpreted with caution. Looking at subgroups of subgroups should be seen primarily as exploratory. Amgen also feels at a disadvantage because they have not had access to all of the analyses being quoted to support the proposed loop diuretic interaction.

Dr. Marciniak stated that patients on digoxin also received less benefit. He noted that you have to look at all factors, heart failure and death endpoints. They behave differently in these trials. Dr. Marciniak proposed that the indicated population should be all of the following:

- Beta-blocker use a maximum or beta-blocker intolerant
- $HR \geq 70$  bpm
- Ischemic etiology only:
  - $HR \geq 75$  bpm
  - On a loop diuretic
- **Drug-Induced Atrial Fibrillation.** Your development program consistently shows a higher incidence of atrial fibrillation with ivabradine treatment compared to control. There appears to be a clear separation in atrial fibrillation occurrence around 6 months in the SHIFT trial. It appears that a medical history of atrial fibrillation is predictive, as expected, of those who will develop atrial fibrillation on ivabradine. When used with ivabradine, the negative chronotropes used to treat and/or prevent atrial fibrillation (e.g., digoxin, beta blockers, and amiodarone) may predispose patients with bradycardia to serious adverse events. This raises the question as to whether ivabradine should be initiated in HFrEF patients with a history of atrial fibrillation who are on additional negative chronotropes for either rate or rhythm control.

**Discussion during meeting:** Dr. Dunnmon stated he appreciated the sponsor's detail in presenting the SHIFT demographic analyses. He explained that it appears that the cardiovascular death (CVD) benefit is confined to the subgroup of patients who could not

tolerate any dose of any beta blocker (BB) in the overall randomized set. This same analysis for beta-blockers approved for the treatment of HFrEF in the United States showed that the CVD benefit was confined to patients tolerating <25% of guideline-directed target doses of these beta-blockers. He requested that the sponsor submit detailed demographic tables (patient demographics as well as disease-related variables) on both of these subsets of patients (those taking no dose of any beta-blocker, and those tolerating less than 25% of target doses for beta-blockers approved in the US). He explained that the Division is very interested in understanding who these patients are, the reasons why they were not tolerant of beta-blocker therapy, the doses of ivabradine these patients ended up taking in SHIFT (e.g., whether it was lower than in the overall population), and the nature of any bradycardia and/or arrhythmic events that may have occurred in these groups as compared to patients taking higher doses of beta-blockers.

Amgen agreed to supply this information and also stated that they would be sending their own publication on BB use in SHIFT for Dr. Dunnmon's review.

**Post-meeting note:** Amgen emailed the publication on December 11, 2014. They indicated they are running the full analysis and will submit when ready.

Dr. Dunnmon stated that ivabradine causes atrial fibrillation, which confers an independent, incremental mortality risk in HFrEF patients. He asked the sponsor to comment on the potential for increased CVD by the induction of atrial fibrillation in HFrEF patients. He further pointed out that patients developing atrial fibrillation in SHIFT were five times more likely to have had a medical history of atrial fibrillation (though in sinus rhythm at randomization). He thus wanted to understand the rationale for treating patients with a history of atrial fibrillation with ivabradine.

Amgen agrees that ivabradine causes atrial fibrillation. It is clear that people who develop atrial fibrillation were five times as likely to have had a history of atrial fibrillation, but stated that patients with a history of atrial fibrillation still demonstrated a benefit with ivabradine therapy. Dr. Dunnmon remained skeptical on this point, noting that the occurrence of atrial fibrillation resulted in the withdrawal of patients from ivabradine therapy in SHIFT, and continued to question the rationale of withdrawing a patient experiencing paroxysmal atrial fibrillation from ivabradine in the clinical trials, but allowing patients with a history of paroxysmal atrial fibrillation to start the drug (understanding they were five times as likely to develop atrial fibrillation on the drug as those without this history). All agree on the need for atrial fibrillation surveillance. Dr. Dunnmon stated he continues to be concerned that the rigor with which this surveillance is (or is not) accomplished may impact the CV outcomes of patients who develop atrial fibrillation in the setting of HFrEF treatment with ivabradine.

- Drug-induced Bradycardia. Ivabradine demonstrates use-dependent block of  $I_f$ , suggesting its effects might be diminished at low heart rates. Thus, it is not surprising that subjects taking guideline-directed target doses of beta-blockers, as well as patients with lower heart rates at baseline, demonstrate limited or no benefit from ivabradine with respect to the SHIFT primary composite endpoint (understanding that higher beta-blocker

doses and lower baseline heart rates are likely related). Conversely, in both SHIFT and BEAUTIFUL, bradycardia SAEs occur predominantly in patients taking one or more negative chronotropes at baseline (e.g., beta-blockers ± digoxin ± amiodarone). We suspect that combinations involving digoxin and amiodarone will be disproportionately confined to those similar to the 22% of SHIFT patients with a medical history of atrial fibrillation at baseline. This raises the same question as noted above: should ivabradine be initiated in HFrEF patients with a history of atrial fibrillation who are on additional negative chronotropes for either rate or rhythm control?

**Discussion during meeting:** Dr. Dunnmon stated that ivabradine causes bradycardia. He noted that higher doses of ivabradine were given in SIGNIFY than SHIFT which resulted in more bradycardia (and according to the sponsor, more bradycardia-associated coronary hypoperfusion) in SIGNIFY. He and the sponsor agree that patients taking combinations of negative chronotropes are going to be more likely to experience adverse events from important bradycardia, and that patients with a history of atrial fibrillation are more likely to be on combinations of negative chronotropes, including not only beta-blockers, but also digoxin and amiodarone. Of note, NDHP calcium channel blockers are a contraindication to ivabradine therapy (purportedly due to drug-drug interactions causing increased levels of ivabradine), but Dr. Dunnmon continues to be skeptical that there is not also a synergistic bradycardic influence of combinations of these drugs, apart from this purported DDI.

- **Background Device Therapy.** As we discussed at the midcycle communication meeting, the virtual exclusion of device therapy from SHIFT limits the ability to determine whether ivabradine therapy provides either a CV death benefit or CV hospitalization benefit to HFrEF patients with CRT or CRT-D devices. We assume there will be no or very limited CV death benefit in HFrEF patients with an ICD. We are interested in your thoughts on how this should be communicated in labeling.

**Discussion during meeting:** No further discussion.

- **Acute renal failure (ARF).** The incidence of serious ARF is higher in subjects treated with ivabradine compared to placebo in SHIFT and BEAUTIFUL. There were also more discontinuations for acute renal failure in ivabradine treated subjects. Preliminary analysis of SIGNIFY does not corroborate this concern. However, subjects in SIGNIFY had a higher mean EF (56%) compared to SHIFT (29%) and BEAUTIFUL (34%). The data suggest that subjects with heart failure may be at risk of renal failure from ivabradine, possibly because their cardiac output is more dependent on heart rate, given their reduced stroke volumes. Please examine the renal failure data more closely and attempt to describe the population who might be at greatest risk for developing ARF from ivabradine. Is it a function of baseline ejection fraction? Is it a function of the change in heart rate? Is it a function of the lowest heart rate they achieved, or the heart rate that was recorded on day 28? Is the occurrence of ARF correlated with the occurrence of atrial fibrillation, due to a decrease in cardiac output from loss of AV synchrony in low-LVEF patients?

**Discussion during meeting:** Dr. Beasley indicated that her remaining clinical safety issues were sent to the sponsor in an information request on December 5, 2014. The sponsor is currently working on a response. Dr. Beasley asked Amgen for their assessment of ivabradine and acute renal failure (ARF).

Amgen has reviewed MedDRA renal failure terms and MedDRA SMQ for renal failure. The data appears balanced between drug and placebo. They saw no evidence of change in eGFR in patients taking ivabradine. They stated that ivabradine increases cardiac output in patients with heart failure and does not cause renal failure.

Dr. Marciniak said that the issue may be with chronic renal failure and not acute. Serum creatinine is a substrate of OCT2 and (b) (4) similar to ranolazine. Increases in serum creatinine were also described in the ranolazine development program. The effect on serum creatinine is small, but it is something that a physician should be made aware of.

Dr. Dunnmon most emphatically takes issue with the argument presented by Amgen that renal failure cannot be caused by low-output states accompanying extremes of heart rate reduction in some patients treated with Ivabradine. He pointed out that:

- Cardiac output is the product of heart rate and stroke volume. In situations where LVEF is a fixed and greatly reduced (likely in the sickest SHIFT patients), cardiac output will obligatorily parallel heart rate. This was seen in both of the sponsor's animal models of ivabradine effects on hemodynamics (rodents and pigs), the hemodynamics from which are reproduced from the Amgen summary of pharmacology for this NDA, for convenience, as follows:

Hemodynamic Effects of Single-dose IV Ivabradine in Conscious Rats

% change vs. pre-drug over 1 h post-dose	Vehicle	ivabradine	
		1 mg/kg iv	10 mg/kg iv
Heart rate	-3±1	-33±2*	-57±9*
MBP	-3±1	-8±1*	-19±3*
Cardiac Index	-3±1	-18±1*	-41±2*
Stroke Index	-2±1	+21±2*	+32±3*
Peak aortic flow	-2±1	+4±1*	+8±1*
dF/dt <sub>max</sub>	-3±1	+2±2*	+6±2*
Total peripheral conductance	+4±1	-10±1*	-28±2*
Central venous pressure	-9±3	+9±2*	+49±8*

Values are mean ± SEM; n=9      \*: p<0.05 vs. vehicle

Effects of Increasing IV doses of Ivabradine on ECG, Hemodynamic and Blood Gas Parameters in Anesthetized Pigs 20 Minutes after Each Dosing

	Mean % changes (vs. pre-drug)							
	Vehicle				ivabradine (mg/kg, iv)			
	1 <sup>st</sup> iv	2 <sup>nd</sup> iv	3 <sup>rd</sup> iv	4 <sup>th</sup> iv	0.03	0.1	0.3	1
Heart rate	-0.1	+1.0	+4.4	+3.5	-6.2	-14.1**	-23.5**	-29.3**
Mean blood pressure	+4.8	+4.6	+8.2	+9.2	+4.0	+4.1	-3.5	-5.5
LVdP/dt	-3.0	-9.3	-13.8	-20.2	-10.1	-17.4	-23.7	-28.5
Cardiac output	-2.0	-7.5	-9.3	-14.3	-8.4	-17.7	-23.8*	-28.3*
Stroke volume	-1.8	-8.1	-11.9	-16.8	-3.4	-3.4	+0.4	+2.7
Total peripheral resistance	+7.6	+13.8	+20.6	+28.7	+11.1	+22.8	+24.1	+28.9
Mean coronary vascular resistance	+10.6	+20.0	+28.2	+44.3	+9.4	+23.6	+33.8	+54.8
Myocardial oxygen consumption	+3.4	+6.4	-0.9	-4.5	-1.5	-11.7*	-21.4*	-31.6*
O <sub>2</sub> delivery / MVO <sub>2</sub> ratio	-1.8	-4.2	-4.6	-7.6	-2.6	-3.4	-5.2	-7.2

n=7-10 \*: p≤0.05, \*\*: p≤0.01 vs. vehicle

- The data from the SHIFT echo sub-study demonstrating a nominally significant placebo-corrected increase in LVEF of 2.7% are limited by the fact that it did not include data from all patients. This was essentially a survivor's analysis of patients who stayed in the sub-study through month 8 (only 411 of the originally included 611 patients). Though the high number of dropouts was similar between the treatment arms, the results of this sub-study cannot be extrapolated to all patients to support the statement that ivabradine improves LV systolic function in all patients.
- The division will be very interested in examining the degree to which heart rate decreased in patients experiencing renal insufficiency in the study to determine if there is a vulnerable subgroup with poor LV performance who do not tolerate extreme (e.g. 30 bpm) decreases in heart rate, which may be manifested as renal hypoperfusion. (b) (4)

3. Discussion of Upcoming Advisory Committee Meeting

**Date of AC meeting:** January 14, 2015

**Date AC briefing package will be sent under separate cover by the Division of Advisory Committee and Consultant Management:** December 22, 2014

**Based on the above-noted concerns, the review team proposes potential questions and discussion topics for AC Meeting as follows:**

1. Ivabradine has one favorable outcome trial in heart failure (SHIFT), one neutral outcome trial in patients with coronary artery disease and systolic dysfunction (BEAUTIFUL), and another neutral overall outcome trial in patients with coronary artery disease but without systolic dysfunction (SIGNIFY), with unfavorable results in a large, pre-specified subgroup. How do these three trials affect confidence in a beneficial effect of ivabradine in heart failure?
2. How do you interpret the observed relationship between ivabradine and loop diuretics for CV mortality?
  - a. How does this finding impact approvability?
  - b. If ivabradine were approved, how does this finding impact labeling?
3. All three trials were conducted outside of the U.S. with hospitalization practices that differ in some regions substantially from U.S. practice. Furthermore, while the benefit regarding HF hospitalizations was highly statistically significant in SHIFT, it was neutral in BEAUTIFUL, and leaning detrimentally in SIGNIFY. How do these findings affect the confidence in an ivabradine benefit for HF hospitalizations?
4. Should HFrEF patients with a history of atrial fibrillation who are on additional negative chronotropes for either rate or rhythm control be initiated on ivabradine?
5. Should HFrEF patients with a history of atrial fibrillation who are not on additional negative chronotropes for either rate or rhythm control be initiated on ivabradine?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

**Discussion during meeting:** The Division stated that the Advisory Committee meeting will most likely be on or around April 14, 2015.

#### 4. Major Labeling Issues

**Section 13.1: “No evidence of mutagenicity or clastogenic activity was observed.”**

For genetic toxicity, the assays with conclusions should be described in this section, though overall there is no concern for potential mutagenicity and clastogenic activity of ivabradine at recommended doses.

**Section: 8.1: Pregnancy**

(b) (4)

**Clinical Pharmacology**

The need to make labeling recommendations with regard to drug-drug interactions more actionable has been relayed to the applicant during the post-midcycle meeting.

**It seems likely that a Medication Guide will be needed as part of labeling.**

**Discussion during meeting:** Labeling was not discussed. Dr. Wu provided the following information post-meeting:

As you plan to revise the labeling to comply with the recently published Pregnancy and Lactation Labeling Rule (PLLR), we have following comments regarding the relevant sections.

For the animal data, it is noted that teratogenic effects are not explicitly stated in the current draft labeling. In pregnant rats treated during organogenesis, embryofetal toxicity and teratogenic effects, characterized by abnormal heart shape, interventricular septal defects, and complex anomalies of primary arteries, were observed at exposures ( $AUC_{24h}$ ) 1 or 3 times of that at MRHD (maximum recommended human dose). There was increased postnatal mortality associated with the cardiac teratogenic effect in rats. We recommend that study findings, especially teratogenicity, be described clearly in the revised labeling.

In addition, considering lethal cardiac teratogenicity in rats and the potential for ivabradine to transfer into placenta and to be excreted in milk, ivabradine should not be given during pregnancy, particularly at the time of the organogenesis of the heart, or during lactation. This conclusion is stated clearly in both the toxicology-written summary (2.6) and the nonclinical overview (2.4), but not included in the current draft labeling. Please revise the labeling accordingly to reflect such contraindications.

## 5. Review Plans

**Discussion during meeting:** It was stated that there will be a 3 month extension on the review clock with a PDUFA date for the end of May. An extension letter will be sent to Amgen with new dates.

## 6. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

# Ivabradine for Heart Failure

## NDA 206-143

### Late Cycle Meeting



Thomas A. Marciniak, M.D.  
Medical Team Leader  
Division of Cardiovascular and Renal Products  
December 10, 2014

# Disclaimer

- The opinions expressed are my data driven professional opinions as an FDA reviewer but are not (yet) the official views of the FDA.

# Advisory Committee Meeting Postponed?

- The AC meeting scheduled for January 14, 2014, will (may?) be postponed until April 2014
- The reason for the postponement is that the issues are complex and the SIGNIFY study results may help to elucidate
- SIGNIFY was submitted too late for a complete review

# Two Major Review Issues

- Inconsistencies among the three trials
- Subgroup interpretations

# Ivabradine Outcome Trials

Trial	Population	N	Results
SHIFT	HF + LVEF $\leq$ 35 + HR $\geq$ 70	6,558	↓↓↓ HF hospitalization; ± ↓ CV death
BEAUTIFUL	Stable IHD + LVEF $<$ 40 + HR $\geq$ 60	10,917	neutral for CV death & HF hospitalization; ↓ MI ?
SIGNIFY	Stable IHD + LVEF $>$ 40 + HR $\geq$ 70	19,102	↑ CV death & MI in symptomatic angina

# Ivabradine Outcome Trials

## *“Inconsistencies”*

Trial	Population	CVD		HF hospital		MI	
		RR	p*	RR	p*	RR	p*
SHIFT	HF + LVEF≤35	0.9	0.1	0.7	<0.001	1.0	0.2
	IHD (68%)	0.9	0.2	0.8	0.003	1.0	0.8
BEAUTIFUL	IHD + LVEF<40	1.0	0.8	1.0	0.9	0.9	0.1
	HR≥70 (49%)	1.0	0.8	1.0	0.8	0.6	0.001
SIGNIFY	IHD + LVEF>40	1.1	0.3	1.2	0.08	1.1	0.4
	symptomatic (63%)	1.2	0.1	1.2	0.2	1.2	0.04

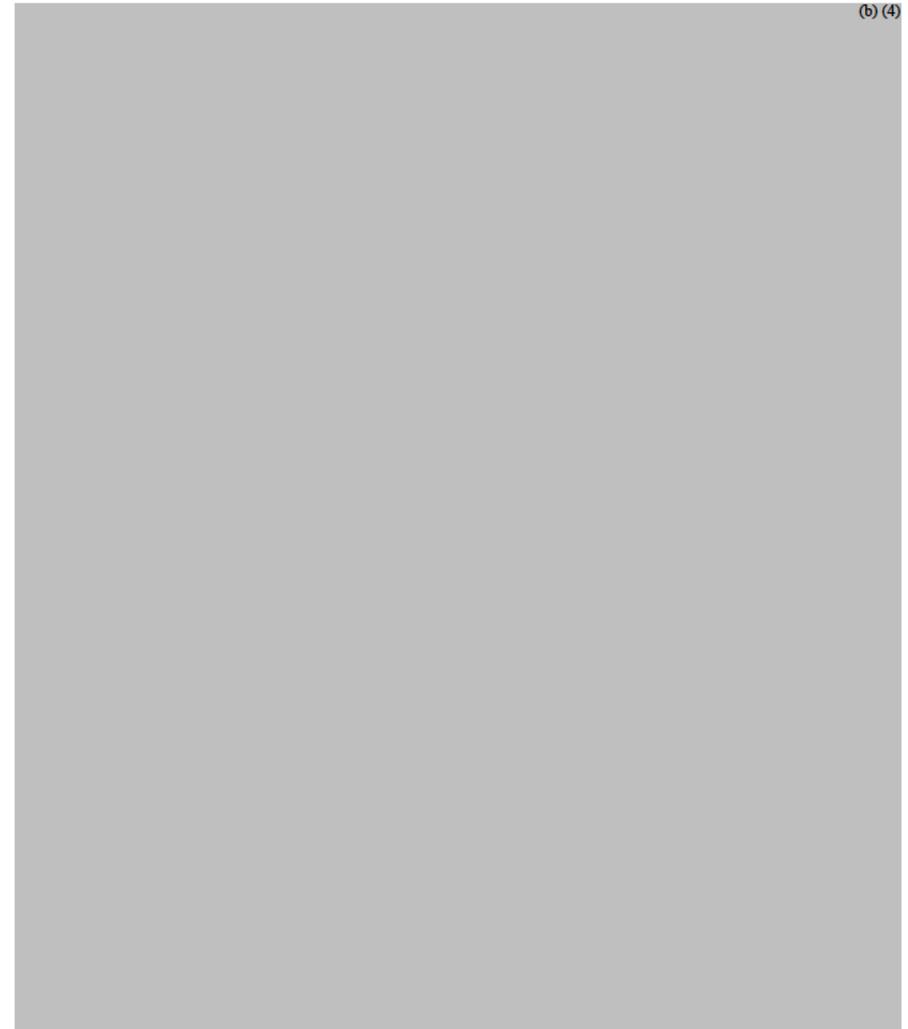
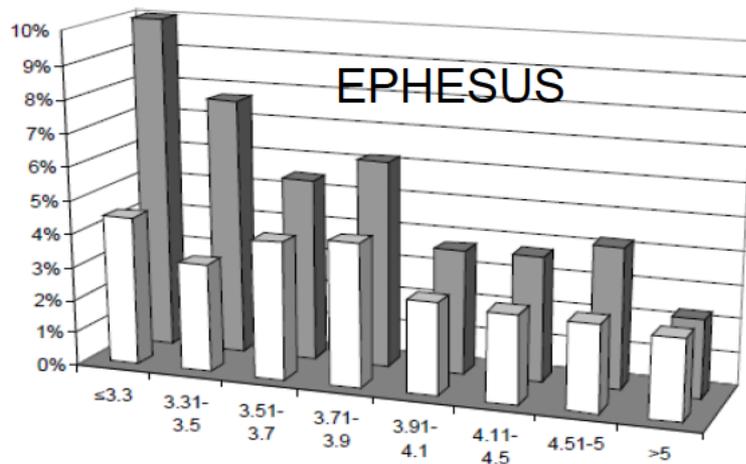
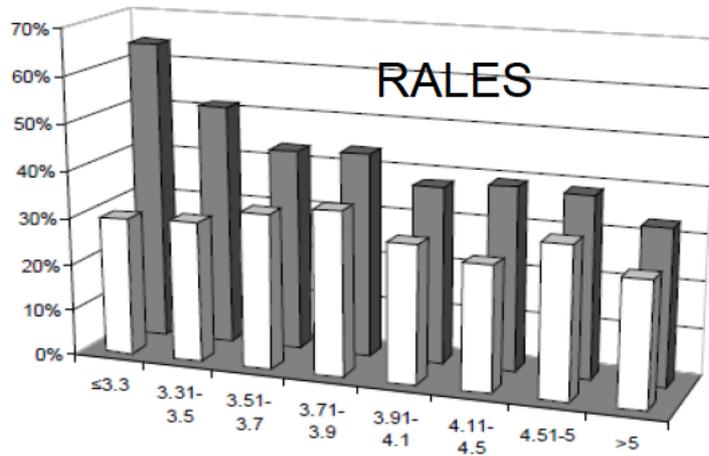
# Factors Explaining the Inconsistencies = Related to Ivabradine Efficacy

- Loop diuretic use
- Heart rate
- Ischemic etiology
- Beta blocker dosage

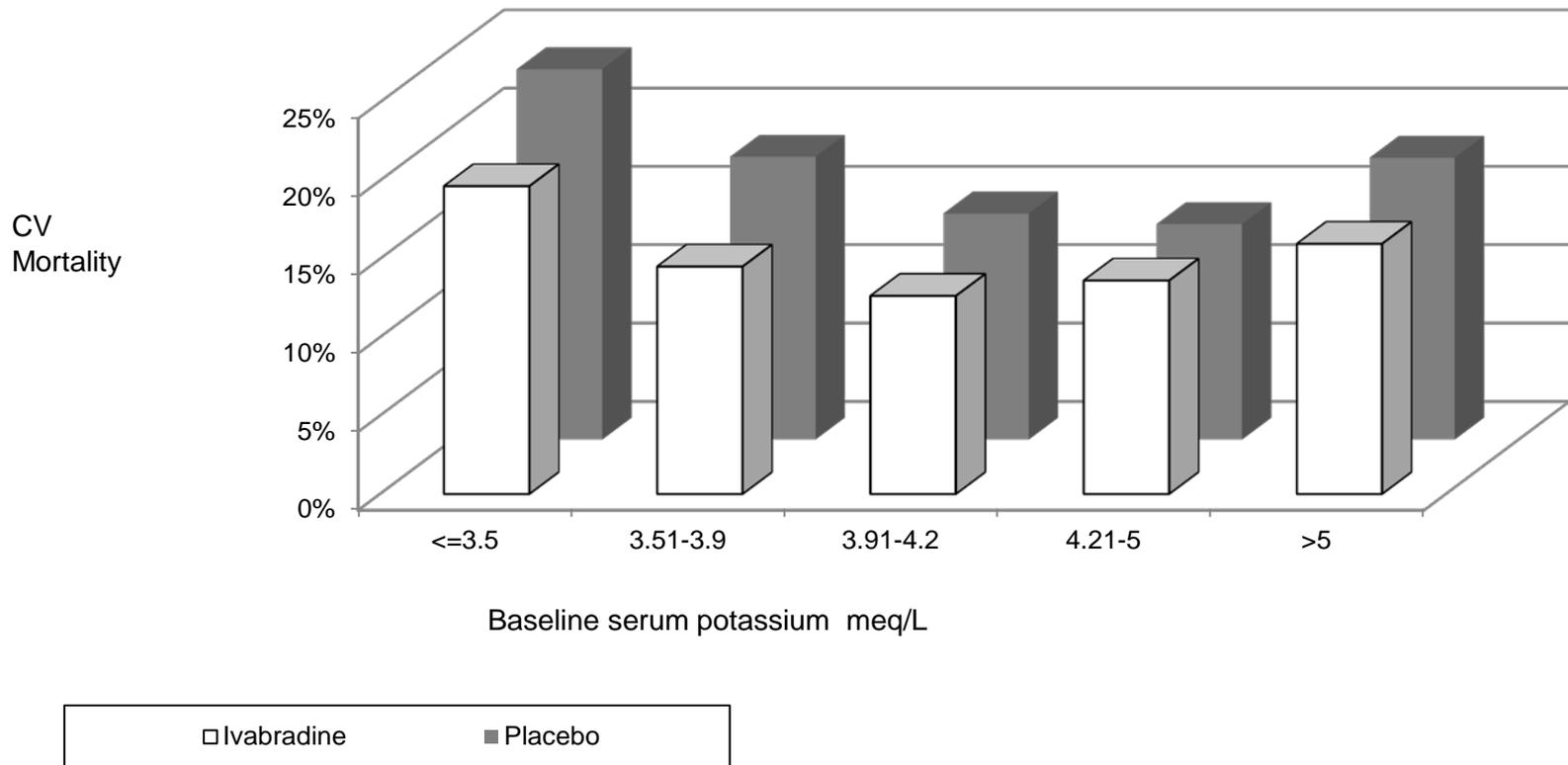
# Concomitant Medications

	SHIFT	BEAUTIFUL	SIGNIFY
BB-any	90%	87%	83%
BB-at target	23%	12%	
MRA	60%	27%	5%
loop diuretic	73%	43%	8%
ACEI	79%	80%	59%
ARB	14%	11%	23%
digitalis	22%	9%	0.5%
statin	57%	74%	92%

# Loop diuretics are 2-edged swords: CV Deaths vs. Baseline K in MRA\* trials



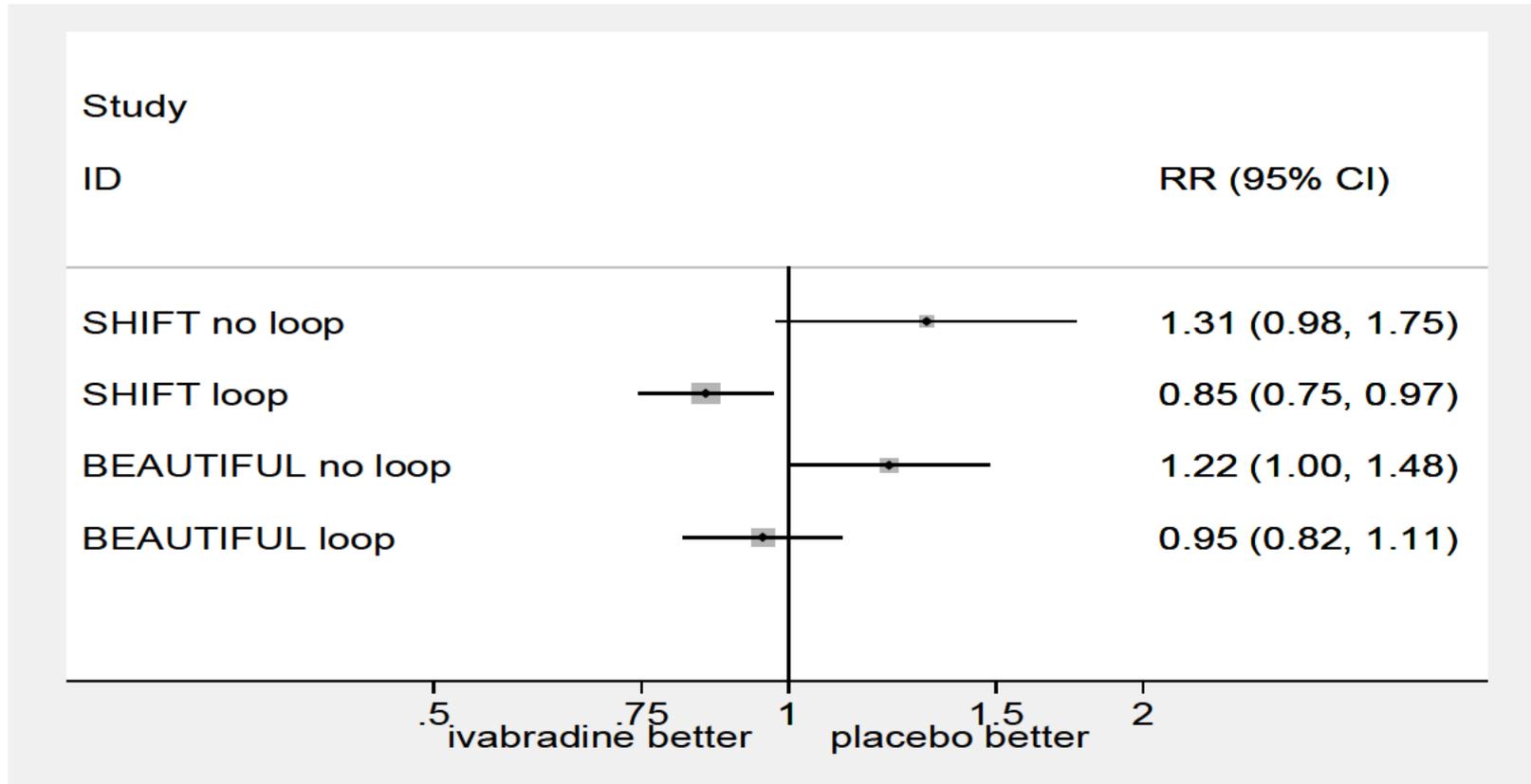
# CV Deaths vs. Baseline K in SHIFT



# Loop Diuretic Use

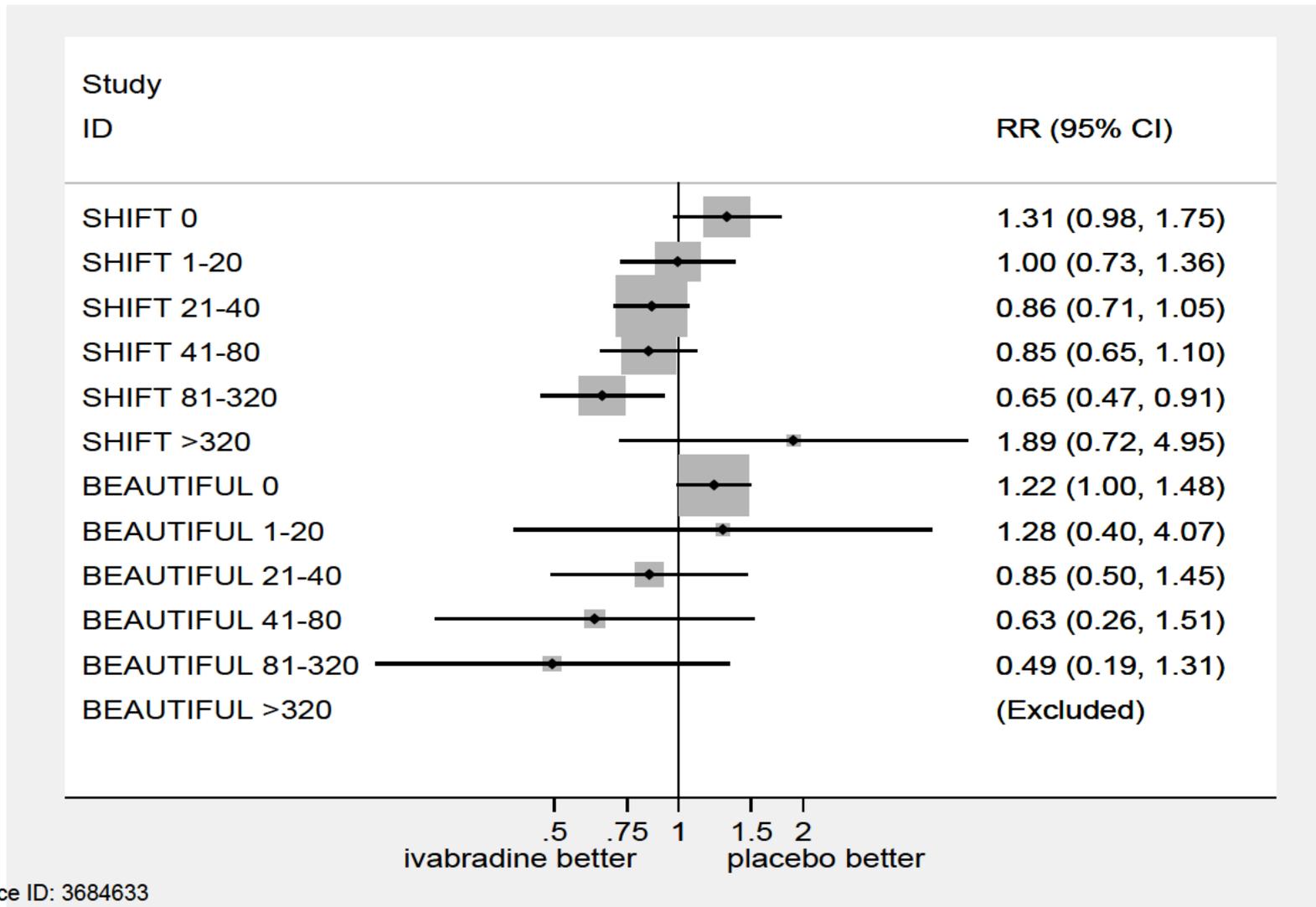
		SHIFT	BEAUTIFUL	SIGNIFY
At randomization	%	73%	43%	8%
	Mean dosage*	43	47	31
Post randomization	%	79%	50%	16%
	Mean max dosage*	87	65	47

# CV Death by Loop Diuretic Use

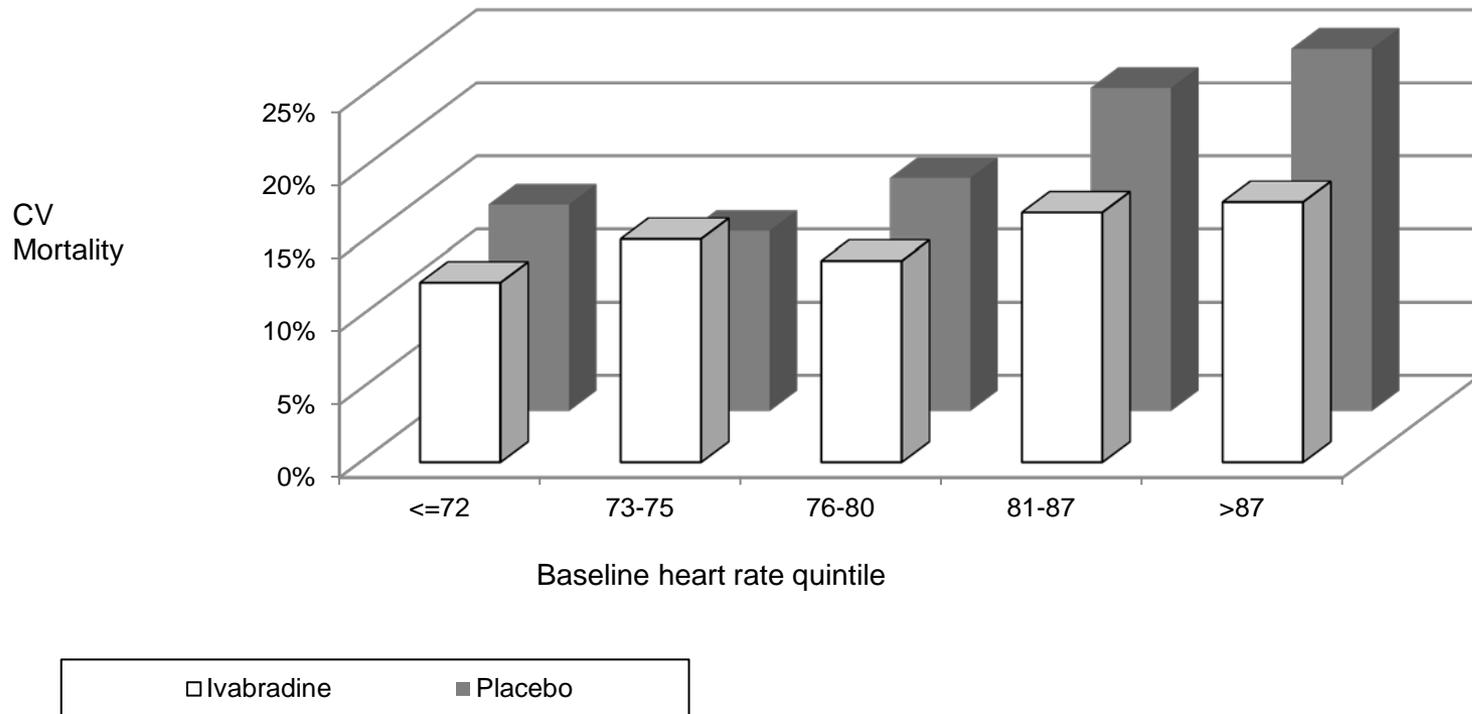


P-values for ivab-loop interaction: 0.007 for SHIFT, 0.054 for BEAUTIFUL

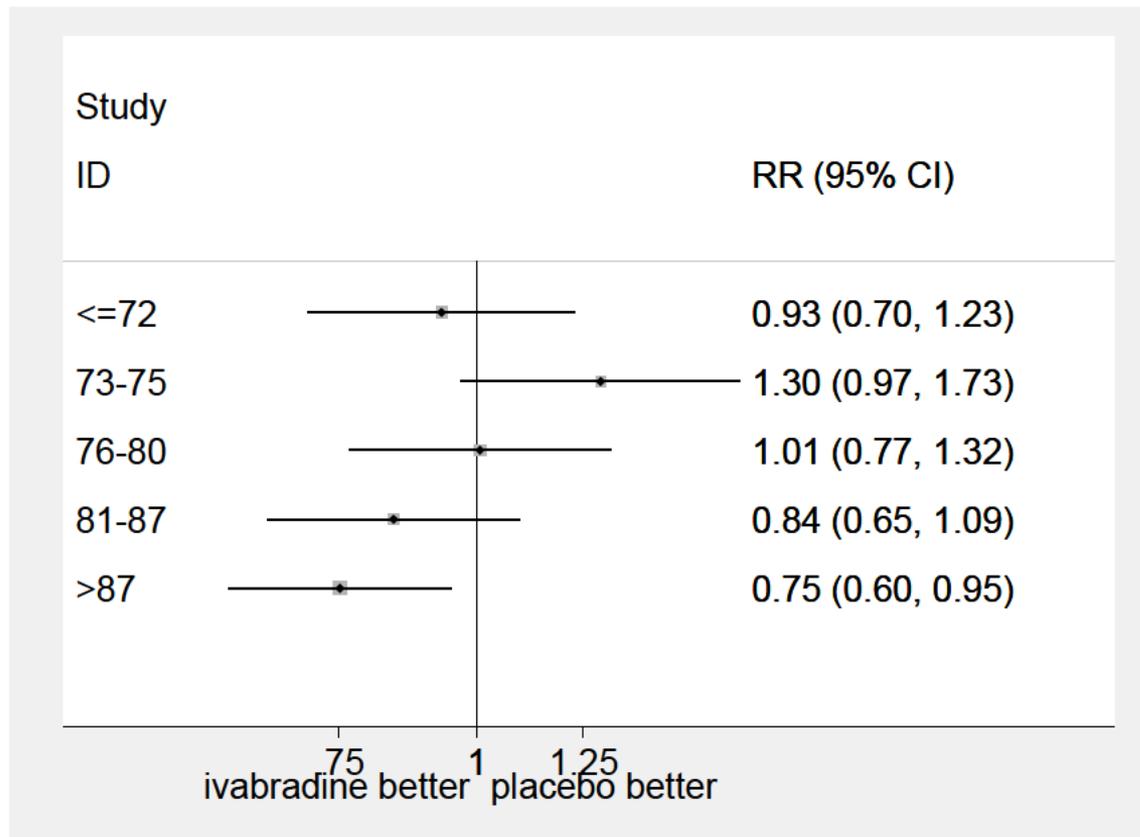
# CV Death by Loop Diuretic Dose



# CV Deaths vs. Baseline HR Quintilein SHIFT

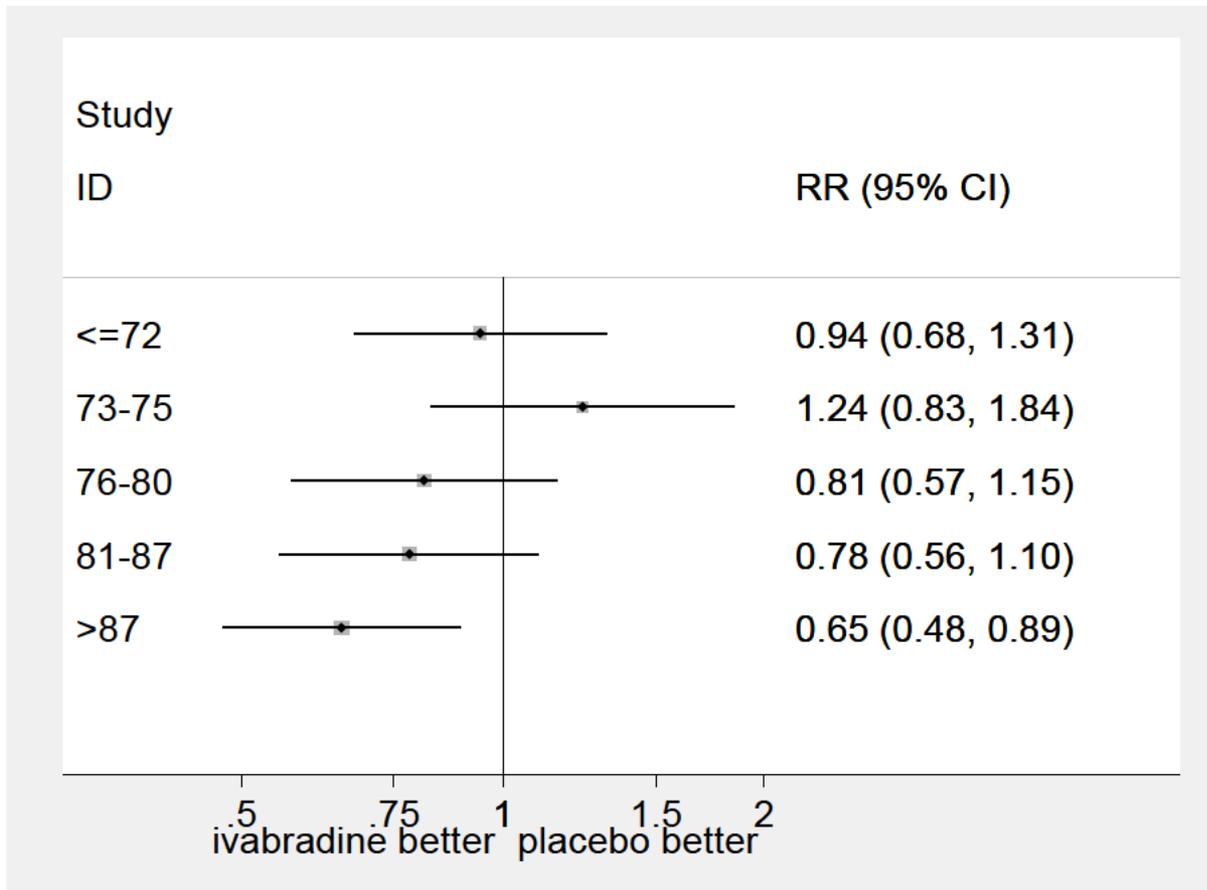


# CV Death Risk vs. Baseline HR Quintile in SHIFT



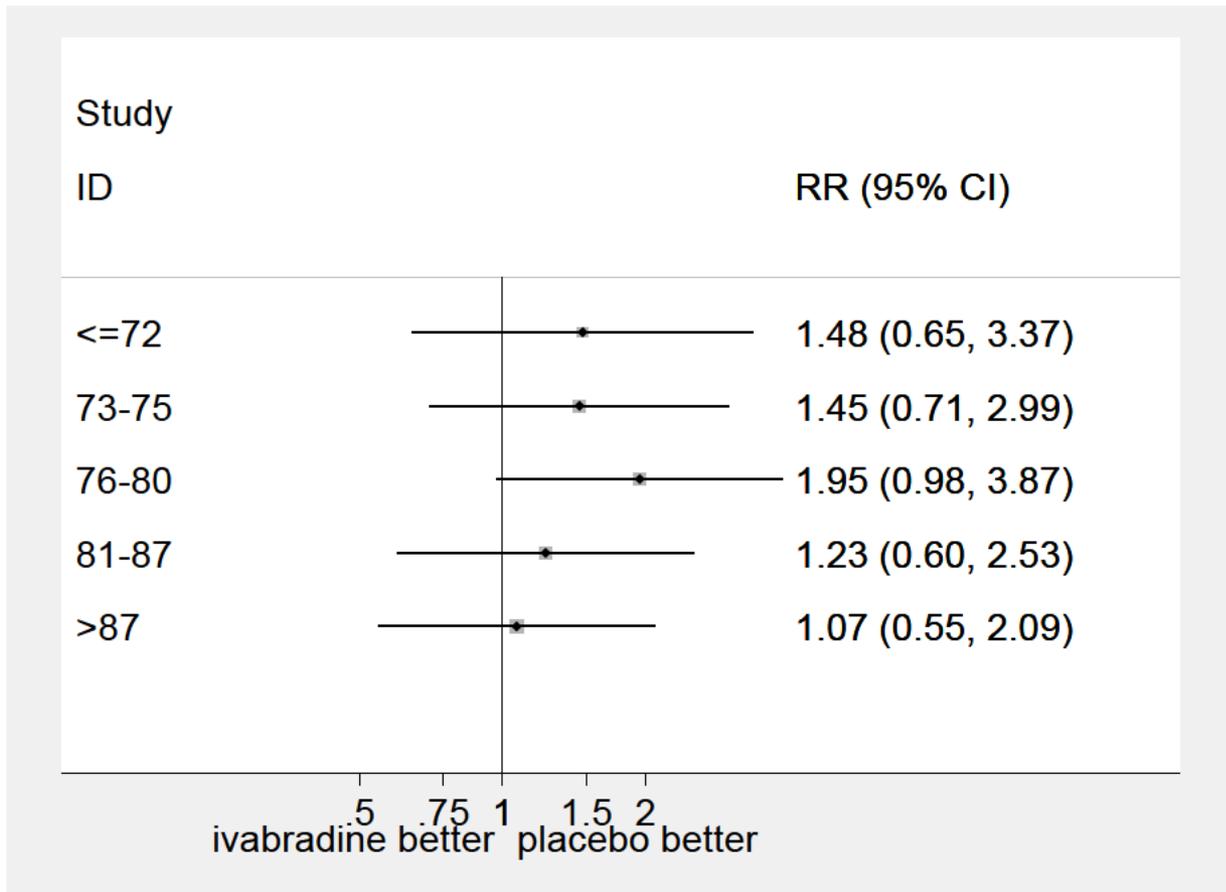
# SHIFT CVD Risk vs. Baseline HR

## SHIFT Ischemic + Loop



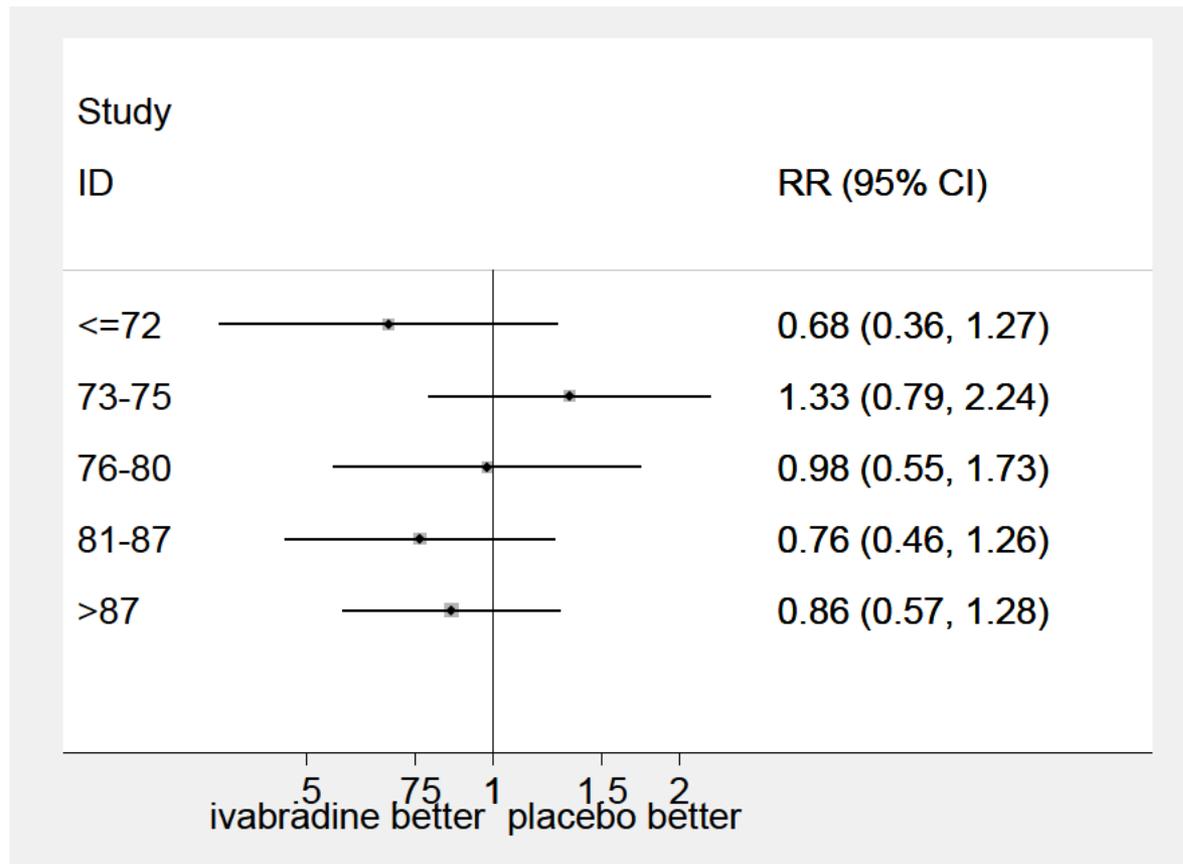
# CVD Risk vs. Baseline HR

## SHIFT Ischemic without Loop



# CVD Risk vs. Baseline HR

## SHIFT Nonischemic

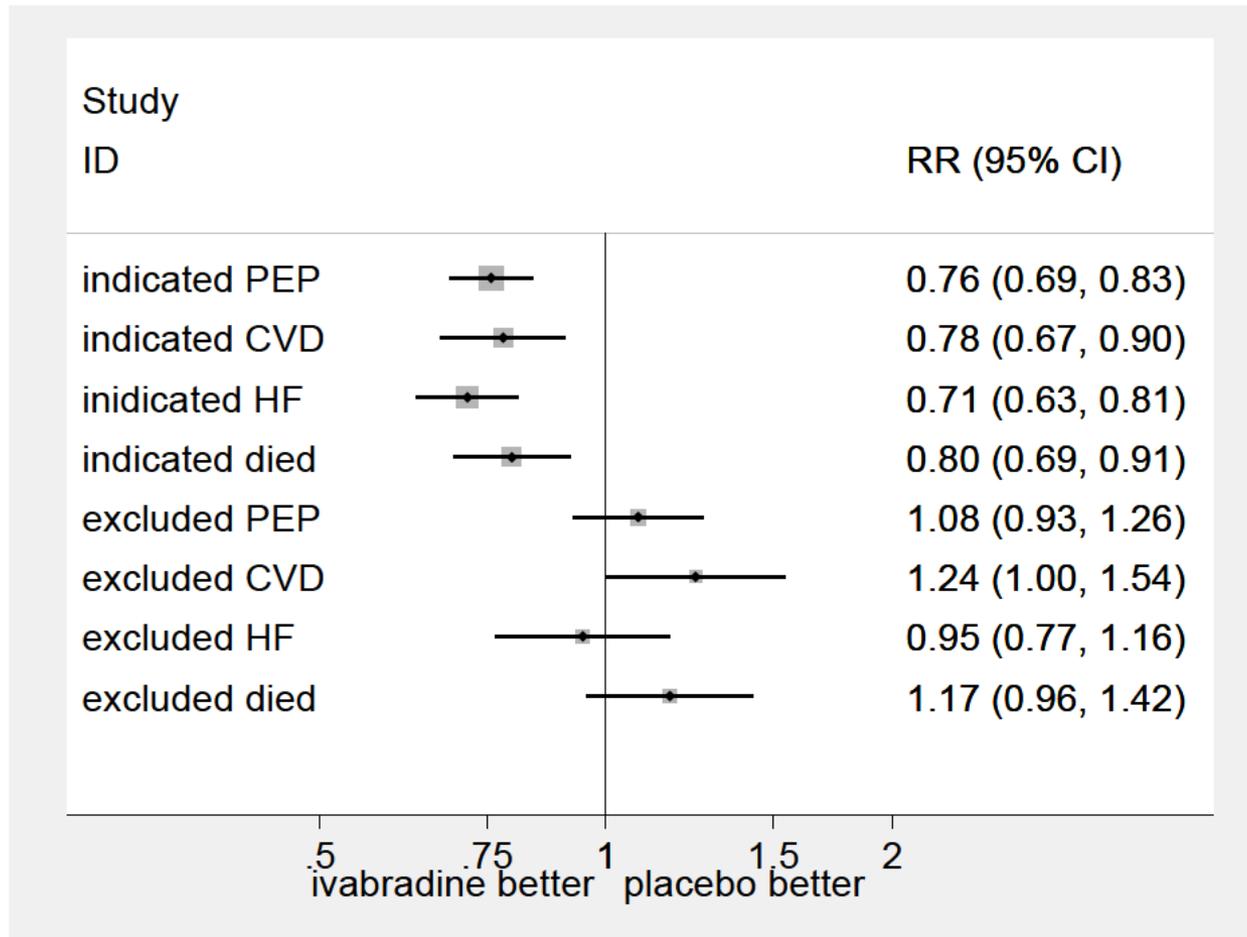


# Proposed Indicated Population

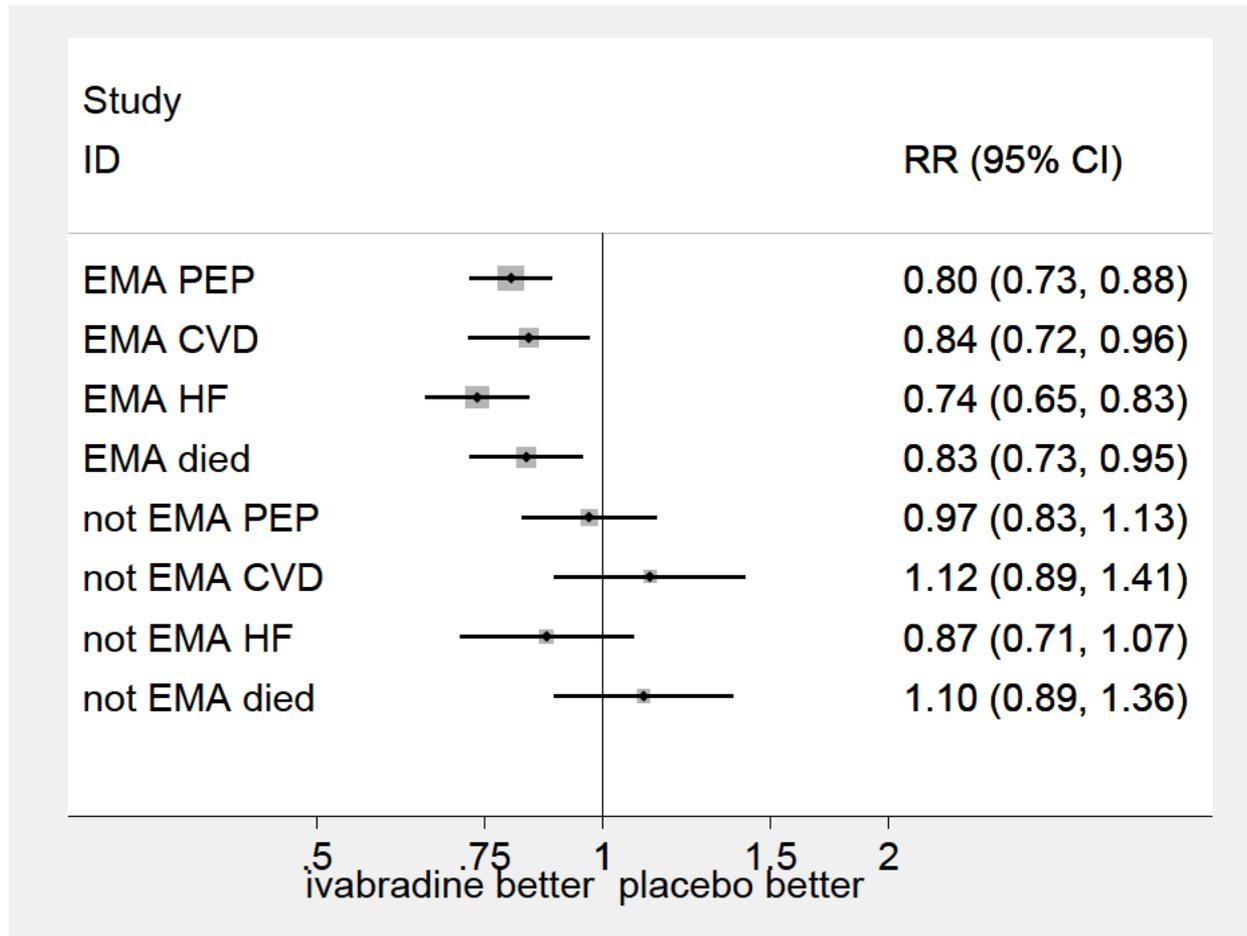
- All of the following:
  - Beta blocker maxed or intolerant
  - HR  $\geq$  70 bpm
  - Ischemic etiology only:
    - HR  $\geq$  75 bpm
    - On a loop diuretic
- SHIFT: 4,020 patients (61%)
- BEAUTIFUL: 1,716 patients (16%)

# EPs in SHIFT & BEAUTIFUL

## Proposed Indicated Subgroup

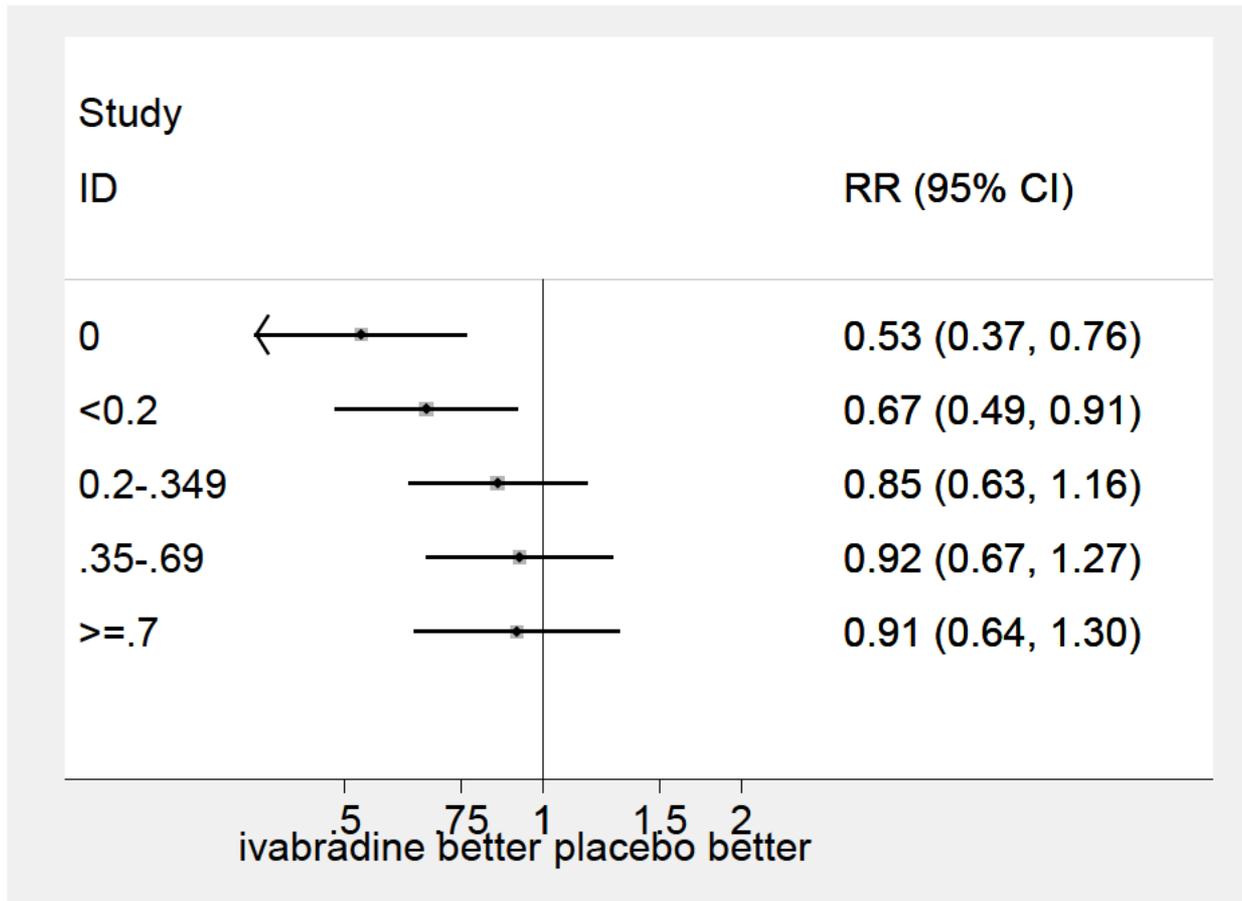


# EPs in SHIFT & BEAUTIFUL HR $\geq$ 75 Subgroup (EMA)

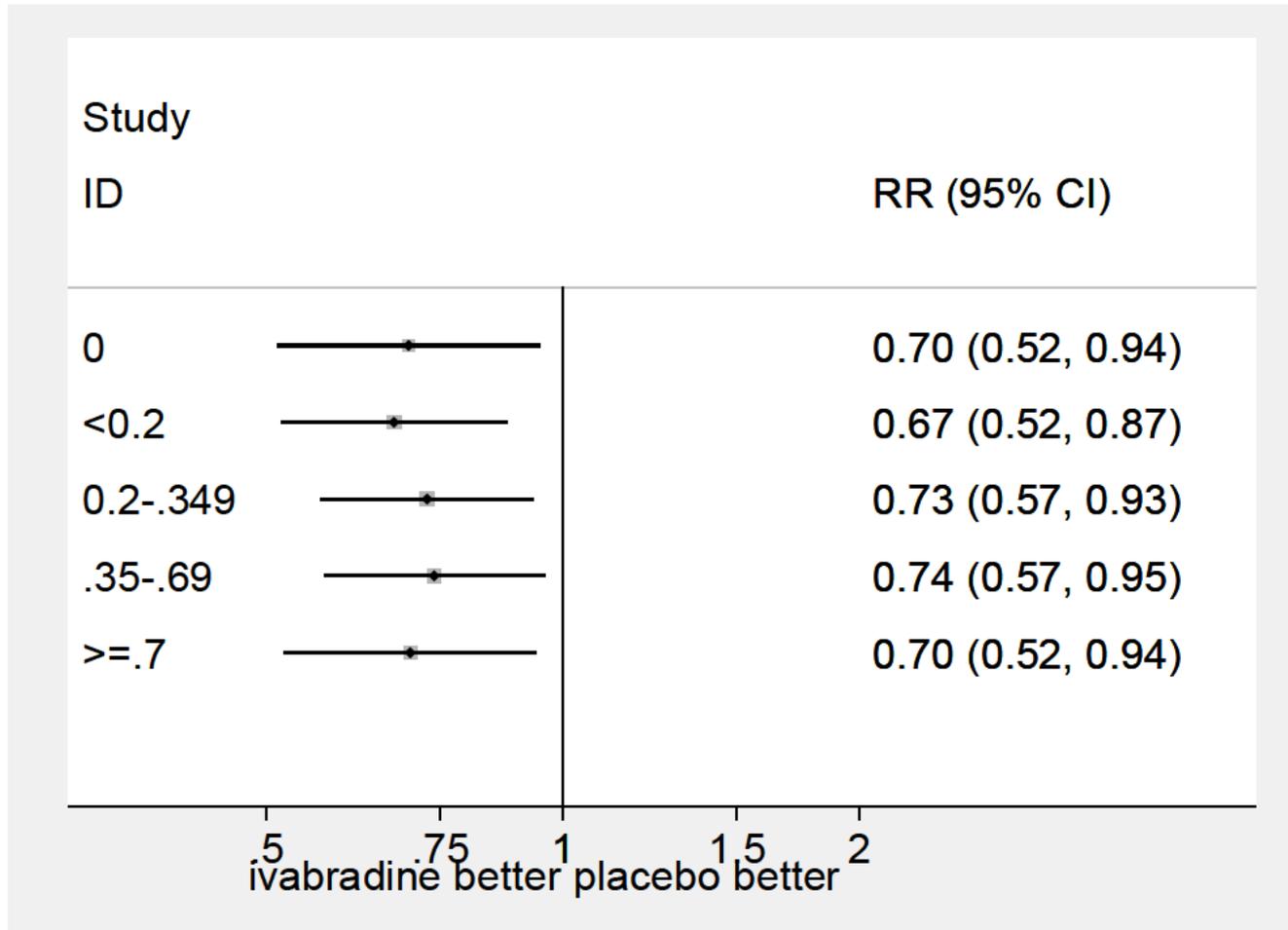


# CVD Risk by Beta Blocker Dose

## SHIFT Indicated Subgroup



# HF Hosp Risk by Beta Blocker Dose SHIFT Indicated Subgroup



# Ivabradine-Digitalis Interaction in SHIFT Primary Endpoint

- Entire study:
  - Interaction OR 1.2,  $p = 0.2$
  - Dig subgroup: OR 0.9,  $p = 0.36$
- Indicated subgroup:
  - Interaction: OR 1.2,  $p = 0.15$
  - Dig subgroup: OR 0.8,  $p = 0.057$

# Indicated Population QED!

- All of the following:
  - Beta blocker maxed or intolerant
  - HR  $\geq$  70 bpm
  - Ischemic etiology only:
    - HR  $\geq$  75 bpm
    - On a loop diuretic
- Benefits:
  - Death -20%
  - HF hospitalization -29%

# Indicated Population!

- All of the following:
  - Systolic HF with LVEF  $\leq 35\%$
  - Beta blocker maxed or intolerant
  - HR  $> 75$  bpm
  - On a loop diuretic
- Benefits:
  - Death -21%
  - HF hospitalization -27%
  - (Stroke -40%)

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/s/  
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NORMAN L STOCKBRIDGE  
01/09/2015



NDA 206143

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Amgen Inc  
Attention: Christine Kubik  
Senior Manager, Regulatory Affairs  
9201 Corporate Boulevard, Suite 400  
Rockville, MD 20850

Dear Ms. Kubik:

Please refer to your New Drug Application (NDA) dated June 27, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ivabradine, 5 and 7.5 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 10, 2014.

Attached is our background package, including our agenda, for this meeting.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** December 10, 2014 1:30-3:00 pm  
**Meeting Location:** White Oak Bldg 22, room 1311

**Application Number:** 206143  
**Product Name:** Ivabradine  
**Indication:** Treatment of heart failure  
**Sponsor/Applicant Name:** Amgen, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive issues that the review team has 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, or 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. As you will see, a number of issues are still under active discussion by the review team.

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:

##### **Clinical:**

- Trial inconsistencies. The inconsistencies among the three Phase 3 trials are concerning. In SHIFT the major benefit of ivabradine was a reduction in heart failure hospitalizations

while results for MI were neutral. In BEAUTIFUL HF hospitalization results were neutral while there appeared to be a benefit for MI. The latter results inspired SIGNIFY, but SIGNIFY failed to confirm a benefit and suggests a detrimental effect in patients with symptomatic angina. We need to understand the reasons for these disparate trial results in order to confirm that there is a benefit in heart failure, and to identify particular subgroups for which benefit may be less.

- Loop diuretic interaction. As communicated on October 6, 2014 during the midcycle communication meeting, the most consistent finding among the three trials is a favorable interaction between ivabradine and loop diuretic use. The interaction is highly statistically significant in SHIFT and suggests a CV mortality benefit of ivabradine in the ischemic patients on a loop diuretic (and the suggestion of a benefit in the non-ischemic patients regardless of loop diuretic use.) In BEAUTIFUL there is a marginally significant interaction for CV mortality, but the effect ranges from no difference with baseline loop diuretic use to a detriment without it. In SIGNIFY there is the suggestion of an interaction for definite CV mortality (excluding unknown deaths) that is significant if post-randomization loop diuretic use is analyzed. A mechanistic explanation of why there is a CV mortality benefit with the interaction in SHIFT whereas there are, at best, neutral results in BEAUTIFUL and SIGNIFY would be helpful. Regardless, the loop diuretic interaction does not explain the differences in HF hospitalizations between the three studies: highly beneficial with ivabradine in SHIFT, neutral in BEAUTIFUL, and leaning negatively in SIGNIFY.
- Drug-Induced Atrial Fibrillation. Your development program consistently shows a higher incidence of atrial fibrillation with ivabradine treatment compared to control. There appears to be a clear separation in atrial fibrillation occurrence around 6 months in the SHIFT trial. It appears that a medical history of atrial fibrillation is predictive, as expected, of those who will develop atrial fibrillation on ivabradine. When used with ivabradine, the negative chronotropes used to treat and/or prevent atrial fibrillation (e.g., digoxin, beta blockers, and amiodarone) may predispose patients with bradycardia to serious adverse events. This raises the question as to whether ivabradine should be initiated in HFrEF patients with a history of atrial fibrillation who are on additional negative chronotropes for either rate or rhythm control.
- Drug-induced Bradycardia. Ivabradine demonstrates use-dependent block of  $I_f$ , suggesting its effects might be diminished at low heart rates. Thus, it is not surprising that subjects taking guideline-directed target doses of beta blockers, as well as patients with lower heart rates at baseline demonstrate limited or no benefit from ivabradine with respect to the SHIFT primary composite endpoint (understanding that higher beta blocker doses and lower baseline heart rates are likely related). Conversely, in both SHIFT and BEAUTIFUL, bradycardia SAEs occur predominantly in patients taking one or more negative chronotropes at baseline (e.g. beta blockers  $\pm$  digoxin  $\pm$  amiodarone). We suspect that combinations involving digoxin and amiodarone will be disproportionately confined to those similar to the 22% of SHIFT patients with a medical history of atrial fibrillation at baseline. This raises the same question as noted above: should ivabradine be initiated in HFrEF patients with a history of atrial fibrillation who are on additional negative chronotropes for either rate or rhythm control?

- **Background Device Therapy.** As we discussed at the midcycle communication meeting, the virtual exclusion of device therapy from SHIFT limits the ability to determine if ivabradine therapy provides either a CV death benefit or CV hospitalization benefit to HFrEF patients with CRT or CRT-D devices. We assume there will be no or very limited CV death benefit in HFrEF patients with an ICD. We are interested in your thoughts on how this should be communicated in labeling.
- **Acute renal failure (ARF).** The incidence of serious ARF is higher in subjects treated with ivabradine compared to placebo in SHIFT and BEAUTIFUL. There were also more discontinuations for acute renal failure in ivabradine treated subjects. Preliminary analysis of SIGNIFY does not corroborate this concern. However, subjects in SIGNIFY had a higher mean EF (56%) compared to SHIFT (29%) and BEAUTIFUL (34%). The data suggest that subjects with heart failure may be at risk of renal failure from ivabradine, possibly because their cardiac output is more dependent on heart rate, given their reduced stroke volumes. Please examine the renal failure data more closely and attempt to describe the population who might be at greatest risk for developing ARF from ivabradine. Is it a function of baseline ejection fraction? Is it a function of the change in heart rate? Is it a function of the lowest heart rate they achieved, or the heart rate that was recorded on day 28? Is the occurrence of ARF correlated with the occurrence of atrial fibrillation, due to a decrease in cardiac output from loss of AV synchrony in low-LVEF patients?

## **ADVISORY COMMITTEE MEETING**

**Date of AC meeting:** January 14, 2015

**Date AC briefing package will be sent under separate cover by the Division of Advisory Committee and Consultant Management:** December 22, 2014

**Based on the above-noted concerns, the review team proposes potential questions and discussion topics for AC Meeting as follows:**

1. Ivabradine has one favorable outcome trial in heart failure (SHIFT), one neutral outcome trial in patients with coronary artery disease and systolic dysfunction (BEAUTIFUL), and another neutral overall outcome trial in patients with coronary artery disease but without systolic dysfunction (SIGNIFY), with unfavorable results in a large, pre-specified subgroup. How do these three trials affect confidence in a beneficial effect of ivabradine in heart failure?
2. How do you interpret the observed relationship between ivabradine and loop diuretics for CV mortality?
  - a. How does this finding impact approvability?
  - b. If ivabradine were approved, how does this finding impact labeling?
3. All three trials were conducted outside of the U.S. with hospitalization practices that differ in some regions substantially from U.S. practice. Furthermore, while the benefit regarding HF hospitalizations was highly statistically significant in SHIFT, it was neutral

in BEAUTIFUL, and leaning detrimentally in SIGNIFY. How do these findings affect the confidence in an ivabradine benefit for HF hospitalizations?

4. Should HF rEF patients with a history of atrial fibrillation who are on additional negative chronotropes for either rate or rhythm control be initiated on ivabradine?
5. Should HF rEF patients with a history of atrial fibrillation who are not on additional negative chronotropes for either rate or rhythm control be initiated on ivabradine?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

## REMS OR OTHER RISK MANAGEMENT ACTIONS

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

### Major Labeling Issues:

#### **Section 13.1: “No evidence of mutagenicity or clastogenic activity was observed.”**

For genetic toxicity, the assays with conclusions should be described in this section, though overall there is no concern for potential mutagenicity and clastogenic activity of ivabradine at recommended doses.

#### **Section: 8.1: Pregnancy**

(b) (4)

### Clinical Pharmacology

The need to make labeling recommendations with regard to drug-drug interaction more actionable has been relayed to the applicant during the post-midcycle meeting.

**It seems likely that a Medication Guide will be needed as part of labeling.**

## LCM AGENDA

1. Introductory Comments – 5 minutes (Alexis Childers –RPM and Tom Marciniak – CDTL)  
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 30 minutes  
Each issue will be introduced by FDA and followed by a discussion.
3. Information Requests – 5 minutes
4. Discussion of Upcoming Advisory Committee Meeting – 25 minutes
5. REMS or Other Risk Management Actions – 5 minutes
6. Major labeling issues – 10 minutes

7. Review Plans – 5 minutes
8. Wrap-up and Action Items – 5 minutes 5

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/s/  
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NORMAN L STOCKBRIDGE  
12/02/2014