CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-051

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT INFORMATION

Pursuant to Supplement NDA 21 CFR 314.53(d)(2) the patent information for this supplement is being submitted concurrently herewith by separate letter addressed to the Central Document Room.

Colleen M. Davenport

Colleen Davenport, Ph.D.
Director Regulatory R&D Regulatory Affairs
Corporate Regulatory Affairs
Sanofi-aventis US

sanofi aventis

U.S. Patent Operations

Central Document Room
Center for Drug Evaluation and Research
Food & Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

James W. Bolcsak
Director
Direct Line: (908) 231-5922
Telefax: (908) 231-2626
james.bolcsak@aventis.com

June 17, 2010

PATENT INFORMATION

Re: NDA 20-839 – Plavix®; Submission of Patent Information for Clopidogrel bisulfate.

Dear Sir/Madam:

The undersigned submits Patent Information including completed Forms FDA 3542a for U.S. Patents No. 4,847,265; and 6,429,210; relevant to the above-referenced submission under Supplemental NDA 20-839.

Pursuant to 21 C.F.R. §314.53(d)(4), two complete copies are attached: one for the Chemistry, Manufacturing and Controls section of the review copy of the NDA, and one to be used as an archival copy. This Patent Information is submitted pursuant to 21 C.F.R. §314.53(c) and (d)(2).

If you should have any questions, please contact me.

Best regards,

James W. Bolcsak, Ph.D., J.D.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

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

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

NDA NUMBER
20-839

NAME OF APPLICANT/NDA HOLDER
sanofi-aventis U.S. Inc. on behalf of sanofi-aventis U.S. LLC

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)
PLAVIX®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Clopidogrel bisulfate	75 mg Clopidogrel bisulfate 300 mg Clopidogrel bisulfate

DOSAGE FORM
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	b. Issue Date of Patent	c. Expiration Date of Patent
4,847,265	July 11, 1989	November 17, 2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
sanofi-aventis	174 avenue de France	
	City/State: Paris	
	ZIP Code: France 75013	FAX Number *(if available)*: +33 1 53 77 41 33
	Telephone Number: +33 1 53 77 40 00	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	1041 Route 202-206, P.O. Box 6800, MailCode D-303A	
	City/State: Bridgewater, NJ	
	ZIP Code: 08807-0800	FAX Number *(if available)*: 908-231-2840
Charlotte Barney	Telephone Number: 908-231-4551	E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.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?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

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

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
James W. Bolcsak	06/17/2010

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 James W. Bolcsak	
Address 1041 Route 202-206, P.O. Box 6800, MailCode D-303A	City/State Bridgewater, NJ
ZIP Code 08807-0800	Telephone Number 908-231-5922
FAX Number *(if available)* 908-231-2626	E-Mail Address *(if available)* james.bolcsak@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 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) Specify the part of the proposed drug labeling that is claimed by the patent.

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.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

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

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

NDA NUMBER
20-839

NAME OF APPLICANT/NDA HOLDER
sanofi-aventis U.S. Inc. on behalf of sanofi-aventis U.S. LLC

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)
PLAVIX®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Clopidogrel bisulfate	75 mg Clopidogrel bisulfate 300 mg Clopidogrel bisulfate

DOSAGE FORM
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	b. Issue Date of Patent	c. Expiration Date of Patent
6,429,210	August 6, 2002	June 10, 2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
sanofi-aventis	174 avenue de France	
	City/State: Paris	
	ZIP Code: France 75013	FAX Number *(if available)*: +33 1 53 77 41 33
	Telephone Number: +33 1 53 77 40 00	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	1041 Route 202-206, P.O. Box 6800, MailCode D-303A	
	City/State: Bridgewater, NJ	
	ZIP Code: 08807-0800	FAX Number *(if available)*: 908-231-2840
Charlotte Barney	Telephone Number: 908-231-4551	E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.com

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

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

PSC Graphics (301) 443-1090 EF

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

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

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
James W. Bolcsak	06/17/2010

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 James W. Bolcsak	
Address 1041 Route 202-206, P.O. Box 6800, MailCode D-303A	City/State Bridgewater, NJ
ZIP Code 08807-0800	Telephone Number 908-231-5922
FAX Number *(if available)* 908-231-2626	E-Mail Address *(if available)* james.bolcsak@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 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) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

EXCLUSIVITY SUMMARY

NDA # 20839 SUPPL # 051 HFD # 110

Trade Name PLAVIX

Generic Name clopidogrel bisulfate

Applicant Name sanofi aventis

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

SE5

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?

6 months

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?

Yes

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# 20839

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 ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES ☐ NO ☒

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

The sponsor conducted the CLARINET trial in patients with with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunts.

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

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

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

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☐	NO ☐

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

Investigation #1

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

n/a

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

The sponsor conducted the CLARINET trial in patients with with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunts.

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

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

Investigation #1		!
		!
IND # 34663	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Alison Blaus
Title: Regulatory Health Project Manager
Date: 3 May 2011

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

ALISON L BLAUS
05/03/2011

NORMAN L STOCKBRIDGE
05/03/2011

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 08/24/2007 (Amendment 1)
Application Written Request was made to: NDA/IND# NDA 02[redacted]39 / IND 034663
Timeframe Noted in Written Request for Submission of Studies: on or before 07/31/2011
NDA# 02[redacted]39 Supplement # 51 (SE5)
Sponsor: sanofi aventis US, LLC
Generic Name: clopidogrel bisulfate Trade Name: Plavix®
Strength: (b) (4) / Dosage Form/Route: Solution (b) (4) for oral administration (This dosage form was used in the efficacy and safety study; it is not proposed for marketing.)
Date of Submission of Reports of Studies: 07/15/2010
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 10/13/2010

Was a formal Written Request made for the pediatric studies submitted?	Y _X_	N __
Were the studies submitted after the Written Request?	Y _X_	N __
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y _X_	N __
Was the timeframe noted in the Written Request for submission of studies met?	Y _X_	N __
If there was a written agreement, were the studies conducted according to the written agreement? ***OR*** **If there was no written agreement, were the studies conducted in accord with good scientific principles?**	Y __	N _X_
Did the studies fairly respond to the Written Request?	Y _X_	N __

SIGNED Mark Roe (Reviewing Medical Officer) DATE 9/24/2010

SIGNED [signature] (Division Director) DATE 9/24/10

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD via Pediatric and Maternal Health Team PM

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection: See Attachment

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date

SIGNED [signature] DATE 11/9/11

1. **Unexpired Patents for Plavix (clopidogrel bisulfate) Tablet; Oral; EQ 75 mg**

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
020839	001	4847265	11/17/11	Yes	Yes	-	-
020839	001	5576328	1/31/14	-	-	U-432	Yes
020839	001	6429210	6/10/19	Yes	Yes	-	-
020839	001	6504030	6/10/19	Yes	-	-	-

DSC: Drug Substance Claim
DPC: Drug Product Claim
U-432: REDUCTION OF ATHEROSCLEROTIC EVENTS (MYOCARDIAL INFARCTION, STROKE, AND VASCULAR DEATH) IN PATIENTS WITH ATHEROSCLEROSIS DOCUMENTED BY RECENT STROKE, RECENT MYOCARDIAL INFARCTION OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

Unexpired Exclusivity for Unexpired Patents for Plavix (clopidogrel bisulfate) Tablet; Oral; EQ 75 mg – None

2. **Unexpired Patents for Plavix (clopidogrel bisulfate) Tablet; Oral; EQ 300 mg**

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
020839	002	4847265	11/17/11	Yes	Yes	-	-
020839	002	6429210	6/10/19	Yes	Yes	-	-
020839	002	6504030	6/10/19	Yes	-	-	-

DSC: Drug Substance Claim
DPC: Drug Product Claim

Unexpired Exclusivity for Unexpired Patents for Plavix (clopidogrel bisulfate) Tablet; Oral; EQ 300 mg – None

Discontinued Drug Products Listing of Unexpired Patents & Exclusivity for Plavix (clopidogrel bisulfate) - None

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

/s/

MATTHEW A BACHO
01/20/2011

JOHN K JENKINS
01/20/2011

DEBARMENT CERTIFICATION

Sanofi-aventis 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.

Colleen M. Davenport

Colleen Davenport, Ph.D.
Director Regulatory R&D Regulatory Affairs
Corporate Regulatory Affairs
Sanofi-aventis US

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 20839 BLA # n/a	NDA Supplement # 051 BLA STN # n/a	If NDA, Efficacy Supplement Type: SE5
Proprietary Name: PLAVIX Established/Proper Name: clopidogrel bisulfate Dosage Form: 0.2mg/kg/day - oral suspension		Applicant: sanofi aventis Agent for Applicant (if applicable): n/a
RPM: Alison Blaus		Division: Division of Cardiovascular and Renal Products

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

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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

❖ Actions	
• Proposed action • User Fee Goal Date is 8May2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Complete Response on 14Jan2011

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

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

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

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

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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] 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.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval and Complete Response Letters Included
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included - No changes
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	n/a
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 n/a n/a
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 14Jan2011 & 6May2011 ☐ DMEPA ☐ DRISK ☐ DDMAC ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	Included ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC n/a If PeRC review not necessary, explain: This application did not trigger PREA and was not reviewed by PERC. • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10May2010 - Minutes dated 26May2010
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 12Jul06
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	28Mar00, 9Aug00, 31Jul08, 5Jan11
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 5May2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	n/a
• Clinical review(s) *(indicate date for each review)*	27Dec2010 & 2May2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	see December 2010 Medical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	n/a n/a ☒ None n/a
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 11Jan2011

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 29Nov2010
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 23Dec2010
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 13Jan2011
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12Jan2011
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

ALISON L BLAUS
05/09/2011

Pediatric Exclusivity Board Minutes

January 13, 2011

Voting Board Members	Review Division/Office	Others
John Jenkins, Chair	Martin Rose	Melissa Tassinari
Lisa Mathis, Deputy Chair	Robert Temple	Matthew Bacho, Board RPM
Dena Hixon	Angelica Dorantes	Denise Pica-Branco
Sally Loewke	Stephen Grant	Rosemary Addy
Renata Albrecht	Alison Blaus	Virginia Elgin
Gilbert Burckart	Norman Stockbridge	Giselle Sholler
	Rajnikanth Madabushi	Sharon Gershon
Advisors	Ramana Uppoor	
Kim Dettelbach	Yeh-Fong Chen	
Dianne Murphy	Edward Fromm	
Robert Nelson		

Determination for Clopidogrel (NDA 020839/S-051)

Initial Written Request:	10/15/01
Amended Written Request:	8/24/07
Timeframe for submission of studies:	7/31/11
Date report of studies submitted:	7/15/10
Due Date for Pediatric Exclusivity Determination:	10/13/10

There were two previous board meetings on clopidogrel (October 5 and November 29, 2010) and since no determination was made regarding Pediatric Exclusivity (PE) a third meeting was held. The Board requested further information concerning Sanofi Aventis' (Sponsor) pediatric program as well as audit findings from the Division of Scientific Investigations (DSI). In addition to the Sponsor's response submitted to NDA 020839 (Supporting Document #327), minutes and letters from the Steering Committee (SC) were also received.

The Written Request (WR), as amended, described two (2) studies to provide data on the use of clopidogrel for the reduction of the incidence of thrombosis in children with systemic-to-pulmonary artery shunts for palliation of cyanotic congenital heart disease.

1. The Sponsor submitted reports on the following pivotal studies:
   - Study 1 (PDY4422 or PICOLO) – A multicenter, randomized, double-blind, placebo-controlled, dose-ranging pharmacodynamic (PD) assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig shunt age categories (neonates and infants/toddlers)
   - Study 2 (EFC5314 or CLARINET) – An international, randomized, double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g., modified Blalock-Taussig shunt)

2. The Chair stated that a determination would be made at this meeting; however, he would give folks an opportunity to appeal his decision, which would then be the responsibility of the Center Director or Deputy Director.
3. DSI summarized their findings from the audits of this supplement:
   - Only one summary report had been finished but all audits came back as NAI or "No Action Indicated";
   - Confirmed the Sponsor's communications, including newsletters, sent to all study sites regarding late randomization times;
   - The reasons for such late randomizations included patient safety and, for one particular site, delays caused by patient transfers between the hospital where surgery took place and another clinic as well as allowing parents two to four weeks to read and sign the Informed Consent Document (ICD); and
   - After reviewing the rationale for these delays, DSI found them plausible.
4. The entire group agreed that a small delay between surgery and randomization could be expected, however, a relaxed approach was used with respect to the ICD. The Review Division (Division) emphasized the Sponsor's decision to avoid admonishing their clinical investigators for such behavior.
5. The Chair noted that a couple of sites did not use aspirin and asked DSI if all sites allowed the use of oral medications. The latter confirmed that fact. The Division then stated that the reasons for starting aspirin in these patients would be sufficient for clopidogrel as well. DSI opined that the investigators' lack of experience with this combination may have prevented them from using it.
6. The Division admitted to the lack of clarity in the protocol for Study 2, such as the failure to adequately define "as soon as possible" with respect to drug randomization. DSI added that clinical judgment was responsible for many of the issues mentioned above, including the patient transfer and ICD procedures. (The NAI decisions mentioned above simply meant that no protocol violations were committed.)
7. The Chair then asked if any new information was found concerning the appropriate dose for Study 2. The Division stated that the SC was not aware of the additional data comparing the pharmacokinetics (PK) of clopidogrel between adults and children. They also emphasized the Sponsor's lack of concern even though some members of the SC and Data Monitoring Committee (DMC) were anxious about the low dose being used.
8. The Chair reminded everyone that the ADP agonist data [originally requested by the Division at the 7/12/06 End-of-Phase 2 meeting] was received and no action was taken. He also noted the Division's original position that they "may reconsider" Study 2 if these data warranted such a decision. The WR clearly required both parties to agree on a dose and the Division sent a vague e-mail to the Sponsor that seemed to agree with the one selected by the latter. The Division noted that Study 2 was started two to three weeks after these events. They added the facts that (1) the Sponsor was aware of these agonist data at the EOP2 meeting and chose not to discuss them and (2) did not adequately identify these data in a subsequent submission for review, reasons that led the Division to question the Sponsor's motives.
9. Ultimately, the Division stated the possibility that these agonist data could have undermined the need for a WR. The Board noted that the WR could have been amended to leave out Study 2. The Division agreed with that possible outcome and,

extending this scenario further, suggested the additional need for more PD data before removing the phase 3 study altogether.

10. Everyone agreed that the Sponsor would have worked harder to find a suitable dose under other conditions (e.g., pursuing an adult claim). The clinical investigators believed that a correct dose was chosen, although they didn't see all of the available PK data. The Division stated that the Sponsor used the Agency to allay any concerns about this matter.
11. With respect to drug randomization, the Board noted the SC's recognition of differences in clinical outcomes between children and adults since many of the shunt failures in the former were due to mechanical issues whereas the latter showed more clotting. Nevertheless, the Division was worried about missing early adverse events since so many children were randomized late to clopidogrel. And while acknowledging the collection of late events, the Division believed they differ from those seen in the first few days after surgery. The Division also noted that mechanically-related events tend to occur earlier than thromboses in these patients.
12. When asked about the SC's subsequent reassurance regarding the timing of these randomizations, the Division saw these developments as a *fait accompli* for everyone involved with Study 2. They were also confused about the reluctance among investigators to coadminister clopidogrel with aspirin since there were no serious safety issues associated with such a regimen.
13. When asked about the formulation(s) used in this program, the Division noted three (3) different ones. They added that no biostudy was included with Study 1 and the bioavailability of the formulation used in Study 2 was never assessed. The latter should have been done although the Division did not expect a substantial difference between it and the adult formulation. In addition to the lower dose, physiological differences between children and adults, due to the relative acidity of the stomach and duodenum, and the use of an NJ tube could have been problematic. This matter was not discussed at the [7/12/06] EOP2 meeting and, under the circumstances, no biowaiver would have been granted.
14. When asked about a population PK analysis of Study 2, the Division stated that nothing was done. They noted that the change in dose and route of administration caused some concern but there was no data to substantiate their position. Sponsors normally conduct such analyses to preclude any anxiety over anticipated differences in bioavailability; however, the Division would not have prevented the Sponsor from using the (b) (4) formulation in Study 2. The Chair pointed out the soft language ("should" and "may") used in the 4th paragraph under "Drug Information" of the WR:

    > "Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults."

15. The Division maintained their stance that PE should be denied. The Sponsor did not meet their standards for conducting a good clinical study since a suitable dose was not selected and clopidogrel was not administered at the time of greatest risk. The Division would not have expected these shortcomings from the Sponsor under other circumstances.
16. The Chair noted that a pharmacologically active dose was arguably achieved in Study 1. He also added that the ADP agonist pathway may not be relevant in this patient

population since the low response could help explain Study 2's outcome (this hypothesis was not specifically tested). The Division noted the differences in drug administration between the two studies and the NJ tube may not have been consistently used.

17 The Chair asked all of the Board members to explain their position on this determination. Those who supported granting PE made the following points:

- The reasons used to justify delay in drug randomization were generally sufficient.
- The Sponsor did communicate their concerns regarding the late randomizations to the clinical sites.
- The dose selection issue was certainly problematic but, aided by some miscommunication, the Division did agree to the one ultimately selected.
- All five (5) sites audited by DSI received an "NAI".
- The WR did not set specific terms on the timing of randomization or bioavailability of the drug.

One who favored denying PE believed that the process for selected a dose was flawed since currently recommended doses of clopidogrel could be 40 times higher than the one used in Study 2. Ultimately, they questioned the scientific integrity of the entire program.

18. The Office of Chief Counsel (b) (5)

19 When asked about targeting the Sponsor for an (b) (5)

.

20. The Chair was disheartened that such a large study in this setting did not provide interpretable data sufficient for labeling. And while the Sponsor was not absolved of their responsibility, the Agency was burdened with writing a good WR. The dose could have been further discussed and the ADP agonist pathway may have been used to stop further study, but an opportunity for adequate follow up was missed despite the timely receipt of data that would have informed these matters. The delayed randomizations in Study 2 were not helped by the amended protocol, which passed without discussion, and it was difficult to argue against the decision to delay administration made by many of the principle investigators. It was unlikely that the new formulation would have affected bioavailability of clopidogrel and the weak WR language made this matter superfluous. In this case, the interpretation of good scientific principles would be subjective, especially given the protocol language. In addition, DSI indicated that there were no protocol violations at any of the sites audited.
21. The Chair decided to grant PE (b) (5)
22. The group discussed a number of ideas that resulted from this experience:

23. The Division noted that a "Complete Response" letter for N020839/051 was due on Friday, January 14, 2011.
24. The group briefly discussed the options of requesting another clinical study in this patient population as well as bringing these issues to a future Pediatric Advisory Committee meeting.
25. The Chair stated that his determination could be appealed by COB Tuesday, January 18, 2011. If none were received by that date then the Sponsor would be notified of his decision soon thereafter.

Addendum

The determination to grant PE went unchallenged.

Recommendations

1. The Board agreed that the Sponsor fairly responded to the WR.
2. Pediatric Exclusivity was granted effective January 20, 2011 (see Checklist signed into DARRTS).
3. The Division will inform the Sponsor via email, utilizing a notification script that Pediatric Exclusivity was granted. The fact that exclusivity was granted will be posted on the pediatric web site along with the WR and any amendments as required by FDAAA (2007), and the exclusivity will be reflected in the next monthly update to the Orange Book.

Prepared by: _____ Date: _____

Deputy Chair: _____ Date: _____

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/s/

MATTHEW A BACHO
03/01/2011

LISA L MATHIS
03/02/2011

Blaus, Alison

From: Blaus, Alison
Sent: Monday, January 24, 2011 12:48 PM
To: Nancy.Kribbs@sanofi-aventis.com
Subject: NDA 20839/S051 - Pediatric Exclusivity Determination

Importance: High

Dear Nancy -

Pediatric Exclusivity has been granted for studies conducted on Plavix (clopidogrel bisulfate), effective 20 January 2011, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080558.pdf).

In accordance with section 505A(e)(1) of the Act, as amended by FDAAA (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made, on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Amendments Act of 2007, requires for one year after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please confirm receipt of this email.

Thank you in advance.
Kind regards,
Alison

Alison Blaus
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
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Food and Drug Administration
alison.blaus@fda.hhs.gov
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Beltsville, MD 20705-1266

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/s/

ALISON L BLAUS
01/24/2011

Pediatric Exclusivity Board Minutes

November 29, 2010

Voting Board Members	Review Division/Office	Others
John Jenkins, Chair	Martin Rose	Elizabeth Durmowicz
Lisa Mathis, Deputy Chair	Robert Temple	Matthew Bacho, Board RPM
Dena Hixon	Shari Targum	
Sally Loewke	Stephen Grant	
	Alison Blaus	
Advisors	Edward Fromm	
Dianne Murphy	Rajnikanth Madabushi	
Julia Dunne	Mehul Mehta	
Elizabeth Dickinson	Kevin Krudys	
Kim Dettelbach	Elena Mishina	
William Rodriguez	Norman Stockbridge	
Robert Nelson	Yeh-Fong Chen	
	Pravin Jadhav	

Determination for Clopidogrel (NDA 020839/S-051)

Initial Written Request:	10/15/01
Amended Written Request:	8/24/07
Timeframe for submission of studies:	7/31/11
Date report of studies submitted:	7/15/10
Due Date for Pediatric Exclusivity Determination:	10/13/10

The initial board meeting for clopidogrel was held on October 5, 2010, and no determination was made regarding Pediatric Exclusivity (PE). The Board decided that Sanofi Aventis (Sponsor) should provide further information about their pediatric program. The following questions were then sent to the Sponsor on 10/13/10:

1. In your protocol for CLARINET you stipulated that subjects were to be enrolled "as early as possible" after shunt surgery. Nonetheless, almost half of the subjects were randomized more than 2 weeks after surgery and 23% were randomized more than 4 weeks after surgery. In a newsletter to the CLARINET investigators dated 31 October 2007, Dr. David Wessel, the CLARINET Steering Committee Chairman, wrote we "have found that more than 50% of patients are randomized more than 2 weeks after palliation surgery. As you may know, the greatest incidence of adverse thrombotic or fatal events after shunt palliation…" Please provide us with details about any efforts you made to encourage investigators to enroll subjects earlier and provide the rationale for the delays in randomization seen in CLARINET. Please explain why you did not amend the protocol to exclude patients who were more than two weeks post-shunt surgery once you became aware of this issue.
2. At the End of Phase 2 meeting held on 12 July 2006, you asked us if additional PD studies were required and in our preliminary response that you received prior to the meeting we asked: "What is the level of platelet aggregation achieved with 5 micrograms [sic] of ADP as a function of age (neonates to adults)?" You did

not provide the requested information at the meeting. According to the meeting minutes, Dr. Stockbridge asked you "to provide data from your platelet inhibition study to show the agonist effect of ADP in neonates. If the response in neonates is similar to that in adults, then the dose range seems reasonable. If it is markedly less than in adults, the premise for the study may need to be reconsidered."

a. Please explain why you believe that a study of administering clopidogrel, an inhibitor of ADP-induced platelet aggregation, to reduce shunt thrombosis at a dose lower than that administered to adults is informative given ADP appears to be a much less potent agonist of platelet aggregation in neonates and infants/toddlers than in adults.
b. You chose to administer a dose of 0.2 mg/kg/day in CLARINET based on the finding in the dose ranging study PICOLO that this dose produced an approximately 50% reduction in inhibition of baseline platelet aggregation in response to 5 μM ADP in neonates and infants/toddlers. This percentage reduction was chosen as a target based on the effect of clopidogrel in adults. Please explain why you believe that method for choosing a dose was appropriate even though the response of platelets to ADP appears to be reduced in neonates and infants/toddlers compared to adults.
c. The reduced response of platelets to ADP in neonates and infants/toddlers might have been expected to have implications for the expected effect size of clopidogrel in CLARINET. Please provide your rationale for the choice of an expected effect size of 30% in light of these data.
d. On October 12, 2006, you submitted to us a document (SN 658 to IND 34663) in response to queries we made at the July 2006 End of Phase 2 meeting. Please disclose to us the date you became aware of the information contained in that submission.

The Sponsor's response was received on 10/25/10 and can be accessed in DARRTS under NDA 020839 (Supporting Document #327).

The Written Request (WR) as amended described two (2) studies to provide data on the use of clopidogrel for the reduction of the incidence of thrombosis in children with systemic-to-pulmonary artery shunts for palliation of cyanotic congenital heart disease.

1. The Sponsor submitted reports on the following pivotal studies:
   - Study 1 (PDY4422 or PICOLO) – A multicenter, randomized, double-blind, placebo-controlled, dose-ranging pharmacodynamic (PD) assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig shunt age categories (neonates and infants/toddlers)
   - Study 2 (EFC5314 or CLARINET) – An international, randomized, double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g., modified Blalock-Taussig shunt)
2. The Review Division (Division) summarized the Sponsor's response to Question #1. The latter's rationale for late randomizations focused on (1) patients being critically

ill and hemodynamically unstable, (2) the possible need for additional invasive intervention, and (3) investigators not wanting to subject parents to the stress of the consent process immediately after major surgery. The Division added that these issues did not appear to greatly inhibit the administration of aspirin, which is normal practice in this patient population. When asked to elaborate on this point, the Division noted that these data were not formally collected but they suspected that the oral form of aspirin was predominantly used.

3. The Board then asked the Division to discuss the Sponsor's stated concern about the increased risk of gut ischemia as one possible reason for delayed randomization. The Division stated that they did not specifically review this issue. The Division was also invited to describe the usual practice regarding initiation of feeding and the use of oral medications in this population. In general, a neonatologist noted that low feedings are administered soon after surgery to assist the gut flora, among other reasons, and gradually increased to full within one to two weeks making the evident delays in randomization of 2 to 4 weeks in some patients seem excessive. In any event, the ability to take anything orally would be evaluated on a patient-by-patient basis. The Division added that neonates usually take aspirin within 3 days of surgery.
4. The Division then summarized the field inspection data on randomizations with a focus on Orlando, FL, and Louisville, KY, where a broad range of delay in time to randomization after surgery (5 to 79 days and 15 to 63 days, respectively) was observed. The Board noted that an audit was still pending on clinical sites in Argentina, which enrolled large numbers of patients.
5. The Division summarized the issues regarding pharmacodynamic (PD) data collected from PICOLO and ADP agonist activity in neonates/infants and adults (Question #2). Based on the Division's original concern regarding the second study, which depended on the relative activity between these two age groups, the Board asked how the Division may have acted if it had known about the difference in 2006. For instance, would the Division have considered a higher dose of clopidogrel for the phase 3 trial or simply determined that ADP was not a relevant pathway in neonates and they not requested the phase 3 trial? The Division noted that it was difficult to answer this hypothetical question and they could not be certain about what their response might have been.
6. The Division also disagreed with the Sponsor's contention that the ADP question at the EOP2 meeting was raised in the context of studying clopidogrel in older children, a matter that had been addressed earlier when it was agreed that it was unnecessary to include anyone other than neonates and infants. In their response, the Sponsor defended their dose selection strategy for the phase 3 trial and stated that it was supported by their consultants.
7. The Chair noted that in the usual case of drug development, where a sponsor is seeking a new indication, the burden is on the sponsor to demonstrate efficacy. However, in the context of pediatric exclusivity, where exclusivity can be granted even if the drug is not shown to be efficacious, the burden for adequate study design falls to FDA in composing the Written Request. He noted that the Sponsor did conduct two clinical trials as requested and the fact that CLARINET involved 900 very sick neonate and infant patients.

8. The Chair noted that the dose selection/ADP agonist matter would be very difficult ground on which to deny PE since the Sponsor submitted the data requested on this issue after the EOP2 meeting and the Division did not provide timely guidance on any changes required for the phase 3 trial. The dose selected for the phase 3 trial met the WR requirement for a 30-50% reduction in platelet aggregation. Others also noted that the PD studies did show an effect of the drug on platelet aggregation and no one could have known for sure that the selected dose would ultimately prove inadequate.
9. The Chair stated that a stronger case for denying exclusivity might be based on the question of whether the Sponsor followed good scientific principles and made reasonable efforts to address the Steering Committee's concerns about late randomization to study drug, which may have made it more difficult to show an effect of clopidogrel in this population (if one exists). In this regard he noted that the WR was not specific on the timing of randomization and that the protocol merely stated that randomization should occur "as soon as possible" after surgery. This would require an assessment of whether the late randomization of patients was reasonable.
10. The Division summarized the events that took place once the Steering Committee (SC) discovered the high frequency of late randomizations: (1) the SC issued a statement in their newsletter to trial investigators; (2) the Sponsor asked trial monitors to encourage clinical sites to enroll patients earlier after surgery; (3) clinical investigators were urged at 3 separate meetings to take such an action; and (4) study coordinator teleconferences also encouraged a change to earlier enrollment. However, the Division informed the Board that no clinical site for CLARINET ever received a targeted communication regarding this issue, which turned out to be the SC's greatest concern. Others pointed out the fact that the SC did not stop the study and the Sponsor did not amend the protocol to require earlier randomization.
11. The Chair inquired about whether CLARINET's protocol was submitted as a Special Protocol Assessment (SPA). The Division noted that the trial was submitted as an SPA; however, there was never full agreement between the Sponsor and Division on the SPA. The Chair inquired about whether the issue of time of randomization after surgery was one of the areas of disagreement and the Division said it was not. The Division did note that the protocol statement regarding randomization timing had been changed from an earlier version requiring randomization within 2 weeks of surgery.
12. The Chair asked if the Sponsor's behavior in this matter was so far from the norm that a case could be made that they did not conduct CLARINET according to good scientific principles. There were varied opinions from those present at the Board meeting on this issue with some arguing that the late randomization and the failure of the Sponsor to act more aggressively was outside the norm and compromised the interpretability of the trial, while others argued that the investigators might have had legitimate reasons for the late randomization. The Division expressed concern that the trial, while negative, might not truly be informative on the merits of use of clopidogrel in this patient population and questioned whether useful information could be included in the product labeling.
13. The group discussed the idea of reviewing case report forms (CRFs) to evaluate how those reasons described under Point #2 affected decisions to start study treatment for individual patients. The Division acknowledged that the Sponsor's reported reasons

of unstable hemodynamic status and the possible need for repeat surgery might be valid in some patients. However, many of those present expressed the view that the issue of wishing to avoid further parental stress due to initiation of the consent process immediately after major surgery has not been substantiated in similar situations. The Chair brought up the established process for reviewing these data [MAPP 6010.6 The Use of Clinical Source Data in the Review of Marketing Applications] using neutral 3rd parties in such instances as well as the lack of precedent for this analysis since it is usually used for endpoints. The group also discussed the possibility of having the Sponsor evaluate the CRFs.

14. The Chair stated that the timing of randomization could have been described more thoroughly in the WR if this was a major concern. The Division and some Board members argued that it is not possible to include every detail of a clinical program in the WR and that a certain amount of faith in the Sponsor's ability to conduct an adequate study was always necessary.
15. When asked for their views on the issue of granting exclusivity, some Board members agreed that the proposition of denying PE based on dose selection and ADP agonist activity was weak. This was not the opinion of other members or their advisors, who stated that children should not be enrolled in a trial where the dose for the conduct of the trial would have been modified by data the Division had requested or the entire trial would have been reconsidered. However, the Board members and some of their advisors expressed concern regarding the issue of late randomization and that this might have undermined the interpretability of CLARINET and indicated the Sponsor's failure to conduct that study according to good scientific principles. They also agreed that more information regarding the Steering Committee's actions as well as the nature and timing of the Sponsor's response, along with their subsequent communications to study participants, should be evaluated.
16. Citing (b) (5) the Office of Chief Counsel (OCC) wondered (b) (5) .
17 When asked about the importance of litigating this case to establish a principle, OCC stated (b) (4)
18 The Chair expressed a desire to review all of the documents on the concerns about late randomizations and the actions take by the SC and the Sponsor, which the Division agreed to provide.
19. The Chair inquired about the ramifications of a continued delay in making a determination regarding exclusivity and OCC noted (b) (5)
20. The Chair stated that granting exclusivity would be reasonable; however, he felt the Board should evaluate additional data, including those requested under Point #18,

before making a decision. He also noted that he would apprise the Center Director about this challenging case.

Addendum

As described in Point #18 above, the Board requested on 11/30/10 the following items from the Division:

1. All minutes of the CLARINET Steering Committee in which the issue of the delay between shunt placement and randomization to the study were addressed.
2. All communications between the Steering Committee and the sponsor and investigators regarding the issue of delayed randomization.
3. Any communications between the sponsor and study sites or study monitors regarding the issue of delayed randomization and any instructions given to encourage earlier randomization at study sites.
4. Any data available to the sponsor regarding the time of initiation of ASA, the route of administration, the amount of delay between ASA initiation and randomization for study drug, and any explanation for the delay. These data will need to come from the sponsor. Perhaps the division could also randomly select a small sample of patients and ask the sponsor to outline their clinical course and the reasons for any delay between initiation of ASA and randomization to study drug. This would be a small sample as a way to "audit" at a high level to better understand the reason for any delay in randomization.

Recommendations

1. A determination could not be made because of the outstanding issues described above.
2. In addition to the information requested (see Addendum), a suggestion was made to wait for an audit of clinical sites located in Argentina before meeting again to discuss the determination, which the Chair would like to do in January 2011.

Prepared by: _____ Date: _____

Deputy Chair: _____ Date: _____

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/s/

MATTHEW A BACHO
01/07/2011

LISA L MATHIS
01/18/2011

Pediatric Exclusivity Board Minutes

October 5, 2010

Voting Board Members	Review Division/Office	Others
John Jenkins, Chair	Martin Rose	Virginia Elgin
Lisa Mathis, Deputy Chair	Robert Temple	George Greeley
Dena Hixon	Yeh-Fong Chen	Rosemary Addy
Gil Burckart	Stephen Grant	Robert Yetter
Sally Loewke	Alison Blaus	Amy Taylor
Charles Ganley	Edward Fromm	Melissa Tassinari
	Rajnikanth Madabushi	Hari Sachs
Advisors		Matthew Bacho, Board RPM
Dianne Murphy		Ruby Leong
Julia Dunne		Allen Rudman
Kim Dettelbach		
Elizabeth Dickinson		
William Rodriguez		

Determination for Clopidogrel (NDA 020839/S-051)	
Initial Written Request:	10/15/01
Amended Written Request:	8/24/07
Timeframe for submission of studies:	7/31/11
Date report of studies submitted:	7/15/10
Due Date for Pediatric Exclusivity Determination:	10/13/10

The Written Request (WR) described two (2) studies to provide data on the use of clopidogrel for the reduction of the incidence of thrombosis in children with systemic-to-pulmonary artery shunts for palliation of cyanotic congenital heart disease.

1. Sanofi Aventis (Sponsor) submitted reports on the following pivotal studies:
   - Study 1 (PDY4422 or PICOLO) – A multicenter, randomized, double-blind, placebo-controlled, dose-ranging pharmacodynamic (PD) assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig shunt age categories (neonates and infants/toddlers)
   - Study 2 (EFC5314 or CLARINET) – An international, randomized, double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g., modified Blalock-Taussig shunt)
2. The Review Division (Division) noted that the Sponsor had failed to follow good scientific principles while conducting their clinical program.
3. The Board asked the Division to present their case so the latter discussed the first major defect in the Sponsor's pediatric program. The PD data from PICOLO indicate that clopidogrel may be a less effective antithrombotic agent in neonates and infants/toddlers than in adults, and there is no indication that these data were taken into account by the Sponsor in planning CLARINET. The CLARINET study used a

dose only one-fifth of the adult dose. At an End-of-Phase 2 (EOP2) meeting [7/12/06], the Division asked about the level of platelet aggregation achieved in 5 μM of ADP as a function of age (neonates to adults) and subsequently requested data from PICOLO to determine the adequacy of the selected dose range. In the absence of any antithrombotic drug, if the platelet aggregation response to ADP is reduced in this age group (neonates to infants/toddlers) then the effectiveness of clopidogrel could be similarly reduced. After receiving [8/8/06] the minutes for this meeting, the Sponsor submitted [10/16/06] a document seeking some clarification regarding the same. Included within this submission was the data the Division had requested but no one reviewed them at the time. The Division believed that these data were not prominent enough to be noticed.

4. The Board then asked the Division what it might have done had these data been reviewed in a timely manner. The Division acknowledged a few possibilities: (1) request an increase the power of CLARINET, (2) conduct another PD study to find a more suitable dose (the Sponsor picked 0.2 mg/kg, which was about one-fifth the adult dose) or (3) reconsider the usefulness of CLARINET.
5. The Division added that very little useful information could be labeled from these two studies beyond the fact that they were performed. Such a conclusion led to an obvious question about the ethics of such a program, especially since the Sponsor never openly discussed the impact of PICOLO on any subsequent efficacy study beyond the following statement in their 10/16/06 submission:

   > "The data show a greater degree of variability in the neonates and infant/toddler group versus the adult population and a decreased responsiveness to ADP in these groups as compared to adults."

6. The Board reiterated the fact that the Division did not review the data from this submission, a curious incongruity since the latter admitted that the document also included language for amending the WR [which they issued on 8/24/07]. When asked if the Sponsor had requested any feedback about this same submission, the Division stated that there may have been an e-mail message but there was uncertainty about a reply. The Board noted that the Division bore some responsibility for this matter.
7. The Division then proceeded to discuss the second major defect in the Sponsor's pediatric program. The high rate of late initiation of clopidogrel in CLARINET was inconsistent with good research practice and may have contributed to the study's negative outcome. The study protocol stated that clopidogrel be initiated "as early as possible following shunt placement" but this did not occur. Such an outcome reduced the power of the study to show a beneficial effect on early thrombotic events.
8. The Division added that the timing of aspirin administration was not captured, which prevented their ability to gauge the patients' receptivity to oral medication (although clopidogrel is designed to be used in intubated patients).
9. The Division emphasized the importance of early thrombotic events, as suggested by the scientific literature, and the failure to administer clopidogrel early in CLARINET. Their view was reinforced by a 10/7/07 message from Dr. David Wessel, MD, Chair of the study's Steering Committee, who strongly recommended that children be randomized as soon as possible after shunt palliation because greater than half of earlier patients had been randomized more than two weeks after initial surgery. The

Division clarified the fact that clopidogrel was consistently administered at the time of randomization, but that randomization was delayed too long after the surgery.

10. Addressing the Division's position regarding the conduct of these two studies, the Board noted that pediatric exclusivity had been denied to (b) (4) on the basis of not following good scientific principles because the ECG strips had not been collected.
11. When asked if the dose from PICOLO had been suitable, the Division stated that it would have been suitable if the caveat they posed had been satisfied, which in this case was the similarity of platelet aggregation in response to 5 µM ADP between neonates/infants/toddlers and adults. The Division believed that these data were available to the Sponsor at the time of the EOP2 meeting but the Sponsor chose not to discuss their possible impact on the pediatric program.
12. With respect to the protocol for CLARINET, the Division noted that it was available at the EOP2 meeting and they found it acceptable.
13. The Division focused on the timing of the randomization and noted that CLARINET's power was ultimately determined by the adverse event rate, which was derived from an observation study done by Li. The latter clearly showed that the majority of events appeared during the first week after shunt placement. The Board noted their impression that the Sponsor did not expect the randomizations to be so late. (The Division added that an audit of CLARINET was ongoing.)
14. When asked for their opinions, other Board members stated that CLARINET was not conducted in an ethical manner. Indeed, the negative outcome predicted by the PICOLO data would allow the Sponsor to avoid labeling the indication. The Division reiterated their inability to substantively label the data from CLARINET, especially given the differences in ADP agonism between age groups.
15. The Office of Chief Counsel (OCC) (b) (5) . The Board then emphasized the joint agreement statement in the WR (Efficacy and Safety Study section):

    "Dose levels for use in this study will be determined by a joint agreement between you and the Division, based upon the dose-response data in the pilot dose ranging study."

    This could be pertinent since the Division did not actually review the PICOLO data. In response, OCC inquired about (b) (5)
16. The Division also acknowledged the Sponsor's attempt to have the randomization done early but neither their efforts nor the Wessel statement (see Point #9 above) did much good. However, the Sponsor was fully aware of the PICOLO data and the early thrombotic events (generally seen under these circumstances) yet decided to proceed with an efficacy and safety study (CLARINET) that would avoid many of the events that were to be measured in the primary endpoint.

17. The Chair concluded that a determination could not be made at this meeting. In the past, sponsors have been asked to address certain issues prior to such decisions so the following questions should be sent to Sanofi Aventis:
    - Why did the Sponsor proceed with the selected dose in CLARINET knowing the differences in ADP agonism between neonates/toddlers/infants and adults shown by PICOLO?
    - Why was the protocol not more specific about the timing of randomization when the scientific literature indicated the predominance of early thrombotic events?
    - Knowing the outcome of PICOLO, why did the Sponsor choose not to sufficiently power CLARINET to show a difference between clopidogrel and placebo?

    Given what we know now, the Board wondered whether the Division would have even requested another study testing clopidogrel in this patient population.
18. The Board expressed concern about the pending patents for clopidogrel and whether any generics could be approved soon.

Addendum

In a message dated 10/5/10 from Dena Hixon, the Office of Generic Drugs verified the fact that a patent is currently blocking any approvals of generic clopidogrel products until November 2011.

Recommendations

1. A determination could not be made because of the outstanding issues described above.
2. The Division agreed to draft the questions mentioned under Point #17 above. These will be submitted to the Board soon for distribution and edits.
3. The Board requested a deadline for the Sponsor's responses. Once those responses are received, another meeting should be scheduled to discuss them.
4. The Chair noted the message from Dena Hixon and stated that the Board had time to fully explore this matter and make the right decision.

Prepared by: _____ Date: _____

Deputy Chair: _____ Date: _____

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/s/

MATTHEW A BACHO
01/07/2011

LISA L MATHIS
01/18/2011

Meeting Minutes

Date:	**5 January 2011**
Application:	**NDA 20839 – S051**
Drug:	**PLAVIX (clopidogrel bisulfate) Tablets**
Sponsors:	**sanofi aventis & Bristol Myers Squibb (BMS)**
Meeting Type:	**Pediatrics (CLARINET) Labeling Discussion with Sponsors**

FDA Participants:

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

Norman Stockbridge, M.D., Ph.D.	Director
Stephen M. Grant, M.D.	Deputy Director
Martin Rose, M.D.	Clinical Reviewer
Edward Fromm, RPh, RAC	Chief Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager

Sanofi aventis Participants:

Rich Gural	VP Global Regulatory Affairs
Nancy Kribbs	Sr. Director Global Regulatory Affairs
Ghislaine Pisapia	Project Direction
Sylvie Fontacave	Clinical Study Director (CLARINET/PICOLO)

Bristol Myers Squibb Participants:

Mathais Hukkelhoven	Sr. VP Global Regulatory Sciences, PV and Epidemiology
Ron Portman, M.D.	Lead, Pediatric Center of Excellence; Pediatric Subject Matter Expert, Cardiovascular/Metabolics
Mel Blumenthal, M.D.	Executive Director; Global Clinical Research - Cardiovascular

Background

Clopidogrel is a platelet P2Y12 ADP-receptor inhibitor currently marketed for treatment of patients with acute coronary syndrome and those with recent MI, recent stroke, or established peripheral arterial disease. The clopidogrel pediatric developmental program was initiated in 2000 to determine if administration of clopidogrel to infants who had undergone systemic-to-pulmonary artery shunt placement for palliation of congenital heart disease would reduce the risk of shunt thrombosis. The sponsor submitted a proposed pediatric study request and the Agency responded with a Pediatric Written Request (PWR) on 15 October 15 2001. After completion of a dose-ranging study in children (PICOLO), the sponsor met with the Division to discuss their planned special protocol assessment (SPA) for the Phase 3 safety and efficacy study (CLARINET). This SPA was submitted on 9 May 2006 and the Division responded with a No Agreement letter on 12 July 2006. Subsequently, the PWR was amended to reflect the agreements. The sponsors met with the Agency on 10 May 2010 for a pre-NDA meeting where a number of aspects of the supplement to the NDA were discussed.

Based on the results of CLARINET, sanofi aventis proposed the following labeling changes in the sNDA submitted as amendment 051 to NDA 20839 on 15 July 2010:

(b) (4)

After review of the supplement by the Division, we proposed (on 14 December 2010) to delete subsection 5.6 and to change subsection 8.4, Pediatric Use, to the following:

> **8.4 Pediatric Use**
>
> Safety and effectiveness in pediatric populations have not been established.
>
> A randomized, placebo-controlled trial neither demonstrated nor ruled out a clinical benefit of administering clopidogrel to neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome include administration of too low a dose of clopidogrel to have an effect and initiation of clopidogrel too long after shunt placement.

On 23 December 2010, sanofi aventis responded to the Division's proposal with the following (which does not differ significantly from their original proposal):

(b) (4)

(b) (4)

This meeting on 5 January 2011 was scheduled to discuss both the Division's and the sponsor labeling proposals and their associated rationale.

Meeting

Dr. Stockbridge began by explaining that the process of determining pediatric exclusivity is directed by Dr. John Jenkins and is separate from the process of revising the label. PREA requires that studies conducted in children to fulfill a PWR be described in labeling, even if a study does not advance our understanding of the drug's utility. Dr. Stockbridge made clear that the Division had concluded that the design and conduct of CLARINET limited the interpretability of the study. While a benefit of administering clopidogrel was not demonstrated, neither was a sizable benefit of administering an appropriate dose at the appropriate time excluded.

The sponsor acknowledged our concerns, but did not think it appropriate to include in the label reasons that might explain why CLARINET failed to demonstrate a benefit because they were speculative. The Division agreed to eliminate the sentence describing possible factors that may have contributed to CLARINET's outcome and proposed the following:

> **8.4 Pediatric Use**
> Safety and effectiveness in pediatric populations have not been established.
>
> A randomized, placebo-controlled trial neither demonstrated nor ruled out a clinical benefit of administering clopidogrel to neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt.

Sanofi-aventis objected to the inclusion of "nor ruled out" and stating that "not demonstrated" summarizes the outcome accurately. The Division noted that some studies are definitive in excluding an important benefit, but CLARINET was not such a study. It is important that the label be worded so that physicians understand that CLARINET does not exclude clinical benefits in children with systemic-to-pulmonary artery shunt.

BMS suggested that it may be appropriate to include language (b) (4) . Sanofi said that they need to discuss the proposed wording with BMS after the teleconference, but plan to return with a counterproposal.

Prior to concluding the teleconference, the sponsors asked whether the Division felt it would be appropriate to insert the name of the study here so that when the results are published, the data could be easily referenced by the reader. The Division agreed that it would be acceptable to note the study name in section 8.4.

Conclusion

Sanofi-aventis and BMS will respond to our new proposal for subsection 8.4 by the end of the week.

Post Meeting Note:
After considering the suggested wording proposed at the 5 January 2011 meeting, Sanofi/BMS responded via email with the following proposal for the label:

(b) (4)

Minutes preparation: _____
Alison Blaus

Concurrence, Chair: _____
Norman Stockbridge, M.D., Ph.D.

Draft: ab 6Jan11
Final: ab 7Jan11

Reviewed:
Fromm 6Jan11
Rose 6Jan11
Grant 6Jan11
Stockbridge 6Jan11

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/s/

ALISON L BLAUS
01/07/2011

NORMAN L STOCKBRIDGE
01/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20839/S-051

INFORMATION REQUEST

sanofi aventis U.S. LLC
Attention: Nancy Barone Kribbs, Ph.D.
Senior Director, Global Regulatory Affairs
9 Great Valley Parkway
Malvern, PA 19355-1304

Dear Dr. Kribbs:

Please refer to your July 15, 2010 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also refer to our correspondence, dated November 30, 2010, requesting additional information needed for our review of your July 15, 2010 request for pediatric exclusivity. In that letter, we requested, "Any data available to you regarding the time of initiation of ASA, the route of administration, initiation of oral feeding, the amount of delay between ASA initiation and randomization to clopidogrel, and any explanation for the delay." Per our phone conversation on December 2, 2010, you indicated that you would provide this information for five CLARINET study centers that we selected. We would like you to provide the following information from the following study centers (their corresponding study center number is in parentheses):

1. Marcelo Felipe Kozak (76503)
2. Estela Horowitz (76502)
3. Andrea De Zorzi (380500)
4. Suresh Joshi (356510)
5. Henri Justino (840006)

The information requested from those sites to address the above-mentioned request from the November 30, 2010 letter would be the following pieces of data:

1. Subject #
2. Date of birth
3. Initial shunt palliation surgery date
4. Start date of post-operative aspirin therapy (by any route of administration)
5. Start date of post-operative aspirin therapy (by mouth or feeding tube)
6. Start date of post-operative feeding by mouth or by feeding tube
7. Daily oral/feeding tube calorie intake, expressed as kcal/kg/day, for each day between start of oral or feeding tube feeding and the date of first dose of study drug (with date)
8. Daily oral/feeding tube fluid volume intake, expressed as mL/kg/day, for each day between start of oral or feeding tube feeding and the date of first dose of study drug (with date)
9. CLARINET randomization date
10. Date of first dose of study drug

11. If the date of randomization occurred after the earlier of the start date of oral or feeding tube administration of aspirin or the start date of feeding by mouth or feeding tube (at any intensity), provide the reason for the delay in randomization.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

NORMAN L STOCKBRIDGE
12/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20839/S051

INFORMATION REQUEST

sanofi aventis U.S. LLC
Attention: Nancy Barone Kribbs, Ph.D.
Senior Director, Global Regulatory Affairs
9 Great Valley Parkway
Malvern, PA 19355-1304

Dear Dr. Kribbs:

Please refer to your July 15, 2010 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We are currently reviewing this submission and are requesting the following information. We request a prompt written response in order to continue our evaluation of your sNDA. Please provide:

1. A list of dates of all CLARINET Data and Safety Monitoring Board (DSMB) meetings (both teleconferences and face-to-face meetings).
2. A list of dates of every CLARINET Steering Committee meetings (both teleconferences and face-to-face meetings).
3. The meeting minutes from every DSMB and Steering Committee meeting. Please also include any information provided to the DSMB and Steering Committee members at these meetings, if such information is not included in the meeting minutes (e.g., slide presentations, data). If these minutes have already been provided, please provide a link or a date of that submission in your response document.
4. All communications between the DSMB and the Steering Committee.
5. A description of the role of the CLARINET Steering Committee.
6. All communications among you, the Steering Committee, the investigators, and the clinical trial monitors regarding the issue of delayed randomization.
7. Any communications between you and study sites or study monitors regarding the issue of delayed randomization and any instructions given about the timing of randomization at study sites.
8. Any data available to you regarding the time of initiation of ASA, the route of administration, initiation of oral feeding, the amount of delay between ASA initiation and randomization to clopidogrel, and any explanation for the delay.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

NORMAN L STOCKBRIDGE
11/30/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20839/S051

INFORMATION REQUEST

sanofi aventis U.S. LLC
Attention: Colleen M. Davenport, Ph.D.
Director, Drug Regulatory Affairs
11 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

Please refer to your July 15, 2010 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

Reference is also made to your correspondence dated July 15, 2010 requesting a determination of exclusivity. We are requesting additional information regarding the studies performed to fulfill the terms of the Written Request. In addition, because of this request for additional information, please be advised that the exclusivity determination will be delayed.

Please provide responses to the following two questions by October 25, 2010:

1. In your protocol for CLARINET you stipulated that subjects were to be enrolled "as early as possible" after shunt surgery. Nonetheless, almost half of the subjects were randomized more than 2 weeks after surgery and 23% were randomized more than 4 weeks after surgery. In a newsletter to the CLARINET investigators dated 31 October 2007, Dr. David Wessel, the CLARINET Steering Committee Chairman, wrote we "have found that more than 50% of patients are randomized more than 2 weeks after palliation surgery. As you may know, the greatest incidence of adverse thrombotic or fatal events after shunt palliation…" Please provide us with details about any efforts you made to encourage investigators to enroll subjects earlier and provide the rationale for the delays in randomization seen in CLARINET. Please explain why you did not amend the protocol to exclude patients who were more than two weeks post-shunt surgery once you became aware of this issue.

2. At the End of Phase 2 meeting held on 12 July 2006, you asked us if additional PD studies were required and in our preliminary response that you received prior to the meeting we asked:

   "What is the level of platelet aggregation achieved with 5 micrograms [sic] of ADP as a function of age (neonates to adults)?"

   You did not provide the requested information at the meeting. According to the meeting minutes, Dr. Stockbridge asked you "to provide data from their platelet inhibition study to show the agonist effect of ADP in neonates. If the response in neonates is similar to that in adults, then the dose range seems reasonable. If it is markedly less than in adults, the premise for the study may need to be reconsidered."

a. Please explain why you believe that a study of administering clopidogrel, an inhibitor of ADP-induced platelet aggregation, to reduce shunt thrombosis at a dose lower than that administered to adults is informative given ADP appears to be a much less potent agonist of platelet aggregation in neonates and infants/toddlers than in adults.
b. You chose to administer a dose of 0.2 mg/kg/day in CLARINET based on the finding in the dose ranging study PICOLO that this dose produced an approximately 50% reduction in inhibition of baseline platelet aggregation in response to 5 µM ADP in neonates and infants/toddlers. This percentage reduction was chosen as a target based on the effect of clopidogrel in adults. Please explain why you believe that method for choosing a dose was appropriate even though the response of platelets to ADP appears to be reduced in neonates and infants/toddlers compared to adults.
c. The reduced response of platelets to ADP in neonates and infants/toddlers might have been expected to have implications for the expected effect size of clopidogrel in CLARINET. Please provide your rationale for the choice of an expected effect size of 30% in light of these data.
d. On October 12, 2006, you submitted to us a document (SN 658 to IND 34663) in response to queries we made at the July 2006 End of Phase 2 meeting. Please disclose to us the date you became aware of the information contained in that submission.

Finally, we request that you preserve all internal and external communications and any other documents about these issues.

If you have any questions, please call:

Alison Blaus
Regulatory Health Project Manager
301-796-1138

Sincerely,

{See appended electronic signature page}

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

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/s/

ALISON L BLAUS
10/13/2010

NORMAN L STOCKBRIDGE
10/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-839/S-051

FILING COMMUNICATION

sanofi aventis U.S. LLC
Attention: Colleen M. Davenport, Ph.D.
Director, Drug Regulatory Affairs
11 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

Please refer to your July 15, 2010 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also refer to your submissions dated August 26, September 8, 9, 15, and 23, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call:

Alison Blaus
Regulatory Health Project Manager
301-796-1138

Sincerely,

{See appended electronic signature page}

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

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/s/

ALISON L BLAUS
09/27/2010

NORMAN L STOCKBRIDGE
09/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-839/S-051

PRIORITY REVIEW DESIGNATION

sanofi aventis U.S. LLC
Attention: Colleen M. Davenport, Ph.D.
Director, Drug Regulatory Affairs
11 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

Please refer to your July 15, 2010 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also refer to your submissions dated August 26, September 8, and 9, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is January 15, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 1, 2011.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-51	SANOFI AVENTIS US LLC	PLAVIX

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/s/

ALISON L BLAUS
09/09/2010

NORMAN L STOCKBRIDGE
09/09/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 20839/S-051

PRIOR APPROVAL SUPPLEMENT

sanofi-aventis U.S. Inc.
on behalf of sanofi-aventis U.S. LLC
Attention: Colleen M. Davenport, Ph.D.
Director, Global Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

We have received your July 15, 2010, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Plavix (clopidogrel bisulfate)

NDA Number: 20839

Supplement number: 051

Date of supplement: July 15, 2010

Date of receipt: July 15, 2010

This supplemental application proposed labeling changes to the 5.6, Warnings and Precautions, Special Populations and 8.4, Use in Specific Pediatric Populations.

Please cite the application number listed above 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

If you have questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20839	SUPPL-51	SANOFI AVENTIS US LLC	PLAVIX

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/s/

EDWARD J FROMM
08/03/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839

Sanofi-Synthelabo Inc.
Attention: Nancy Barone Kribbs, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Reference is made to your November 6, 2000 Proposed Pediatric Study Request for Plavix (clopidogrel bisulfate) submitted to IND 34,663.

To obtain needed pediatric information on clopidogrel the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the studies in pediatric patients described below.

STRATEGY

The requested data will provide guidance for the use of clopidogrel in the reduction of the incidence of thrombosis in children with modified Blalock-Taussig shunts for palliation of cyanotic congenital heart disease. The following pediatric development plan will implement this goal:

1. Performance of a steady state phamacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the Blalock-Taussig shunt (neonate and infant/toddler). This trial will provide for the selection of an appropriate dose for an efficacy and safety, placebo-controlled study in patients with Blalock-Taussig shunts.

2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with Blalock-Taussig shunts.

3. Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing Blalock-Taussig shunt placement, as well as a comprehensive safety evaluation of clopidogrel use in children. The safety evaluation in children receiving clopidogrel should include more than a summary of the published literature and include formal analyses of the available published and unpublished safety information. Examples of sources for unpublished safety information include institutions or organizations that systematically collect such data as part of their healthcare delivery to pediatric populations.

PEDIATRIC AGE GROUPS

The five pediatric age groups that we refer to in this document are:

1. Neonates (age less than one month).
2. Infants and toddlers (age 1-24 months).
3. Pre-school children (age 2-6 years).
4. School-age children (age 6 to Tanner Stage 3).
5. Adolescents (Tanner Stage 3 to 16 years).

FORMULATION ISSUES

The studies described below should use an age-appropriate formulation of clopidogrel. The relative bioavailability of this formulation should be determined, compared with the marketed formulation of clopidogrel. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances, the use of a solid dosage form suspended in food or other formulations can be used, if it is standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

TRIAL DESIGN AND GENERAL CONSIDERATIONS

DOSE-RANGING PHARMACOKINETIC/PHARMACODYNAMIC STUDY

Pharmacodynamic data should be obtained from a dose-ranging study in pediatric patients with therapeutic shunts of any kind who are in the efficacy population age groups (neonates and infants/toddlers). The goal of this study is to identify a dose providing steady state inhibition of platelet aggregation similar to that observed in adults taking clopidogrel (*i.e.*, 30 to 50% inhibition of ADP-induced platelet aggregation). The initial three doses used in the study should provide a 10-fold difference between dose levels. However, if the lowest dose group provides little or no effect in the first few patients, modification of this dosing plan is acceptable in order to establish more rapidly doses of clopidogrel with effects on platelet aggregation in the population. The results of this study will be the basis for the choice of the single dose to be used in the efficacy and safety study.

If the neonates and infants/toddlers have PD findings similar to those in adults, no further PD studies in the three older pediatric age groups (pre-school, school-age, and adolescent age) will be required. If additional studies are required, the single previously determined dose may be used for the older age groups, and the study may proceed in parallel to the planned efficacy and safety study in the neonates and infants/toddlers (see below). As the use of therapeutic shunts is rare in the pre-school, school age and adolescent-age populations, additional discussions about the numbers of patients required in these age groups may be necessary.

EFFICACY AND SAFETY STUDY

An efficacy and safety study that would be considered responsive to this request will be a placebo-controlled, double-blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a modified Blalock-Taussig shunt for palliation of congenital heart disease. Patients should be randomized to clopidogrel (once per day at the determined dose) or to placebo following shunt

placement, and then treated up to the time of the next surgical procedure for correction of their congenital heart disease. Blood samples should be obtained in a sufficient number of subjects to analyze the population pharmacokinetic (PK) and PD profile for the chosen dose of clopidogrel, with PK based on the levels of the inactive metabolite of clopidogrel. Sparse sampling methodology can be used, provided sufficient samples are obtained at four times (one before peak serum concentrations, two following the peak, and one at or around the time of peak concentrations). Use of concomitant medications to prevent stent thrombosis should be left to the discretion of individual investigators.

The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations. A relative risk reduction of 30% is acceptable, but the study must be powered using objective clinical data demonstrating a realistic event rate for the primary endpoint, which is the combined incidence of any death, shunt thrombosis requiring intervention, and hospitalization for bi-directional Glenn procedure (prior to four months of age). The study should be designed with at least 80% power to detect a treatment effect at a conventional level of significance (p=0.05).

The study need not demonstrate that clopidogrel is effective at reducing the incidence of the primary endpoint when used in pediatric patients who undergo a modified Blalock-Taussig shunt placement, but it must be interpretable.

RECRUITING

Both the dose ranging and the efficacy/safety studies should be performed in patients of both sexes in the pediatric age groups above, approximately evenly distributed among the relevant pediatric age groups. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.

FORMAT OF REPORTS

Full study reports of the requested studies should be submitted as a supplement, including full analyses, assessments, and interpretations of the primary data.

LABELING CHANGES

The results of the completed studies may be used in the labeling of clopidogrel to add information allowing proper dosing for safe and effective use in the prevention of thrombosis in children with Blalock-Taussig shunts. A new indication will be approved only if the studies demonstrate safety and efficacy in the pediatric population studied that is distinct from the currently approved uses of clopidogrel.

TIMING OF SUBMISSION OF REPORTS

Reports on the above studies must be submitted to the Agency on or before 10 years from the date of the letter. Pediatric exclusivity only adds to the existing patent protection or exclusivity that has not expired at the time the study reports are submitted in response to this Written Request.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC**

EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Also, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please call:

Ms. Colleen LoCicero
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Rachel Behrman, M.D., M.P.H
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Rachel Behrman
10/15/01 08:38:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 1

NDA 20-839

Sanofi-Aventis
Attention: Nancy Barone Kribbs, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Please refer to your correspondence dated October 12, 2006 (serial #658), requesting changes to our
October 15, 2001 Written Request for pediatric studies for Plavix (clopidogrel bisulfate).

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated October 15, 2001.

This Written Request contains a mixture of requirements (failure to fulfill these would result in denial of exclusivity) *and* advice. We have highlighted formal requirements to make this distinction clear.

STRATEGY

The requested data will provide guidance for the use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease. The following pediatric development plan will implement this goal:

1. Performance of a steady-state pharmacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the systemic to pulmonary artery shunt (neonates, age < 1 month, and infants/toddlers, age 1-24 months). This trial will provide for the selection of an appropriate dose for an efficacy and safety, placebo-controlled study in patients with systemic to pulmonary artery shunts.

2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with systemic to pulmonary artery shunts.

3. Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing systemic to pulmonary artery shunt placement, as well as a comprehensive safety evaluation of clopidogrel use in children. The safety evaluation in children receiving clopidogrel must include more than a summary of the published literature and include formal analyses of the available published and unpublished safety information. Examples of sources for unpublished safety information include institutions or organizations that systematically collect such data as part of their healthcare delivery to pediatric populations.

TRIAL DESIGN AND GENERAL CONSIDERATIONS

DOSE-RANGING PHARMACOKINETIC/PHARMACODYNAMIC STUDY

Pharmacodynamic data must be obtained from a dose-ranging study in pediatric patients at risk for thrombosis (including patients with therapeutic shunts of any kind) and who are in the same age range (neonates and infants/toddlers) as patients in the efficacy study. The goal of this study is to identify a dose providing steady state inhibition of platelet aggregation similar to that observed in adults taking clopidogrel (*i.e.*, 30 to 50% inhibition of ADP-induced platelet aggregation). The initial three doses used in the study must span a 10-fold range; however, if the lowest dose group provides little or no effect in the first few patients, modification of this dosing plan is acceptable in order to establish more rapidly which doses of clopidogrel have effects on platelet aggregation in the population. The results of this study will be the basis for the choice of the single dose to be used in the efficacy and safety study.

EFFICACY AND SAFETY STUDY

Dose levels for use in this study will be determined by a joint agreement between you and the Division, based upon the dose-response data in the pilot dose-ranging study.

This must be a placebo-controlled, double-blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients must be randomized to clopidogrel (once per day at the determined dose) or to placebo following shunt placement, and then treated up to the time of the next surgical procedure for correction of their congenital heart disease. The study drug must be stopped in the following situations:

- Occurrence of any component of the primary efficacy endpoint
- The next surgical procedure is to be carried out
- Discontinuation is needed for management of an adverse event
- The parents or guardian request withdrawal
- The investigator decides that discontinuation is in the best interest of the patient

As there is no standardized care in this patient population, additional therapy must be in accordance with the usual practice of the institution (*i.e.* plus or minus concomitant aspirin).

The primary efficacy endpoint is the first occurrence of any component of the primary composite endpoint of:

- Death from any cause
- Shunt thrombosis requiring intervention, or
- Hospitalization for bi-directional Glenn procedure or any cardiac related intervention prior to 120 days of age following an event or a shunt narrowing considered thrombotic in nature.

STATISTICAL CONSIDERATIONS

Since there are closely related indications in adults, a claim in children would be supported by one study with an observed effect on the primary end point significant at $p < 0.05$. Your initial estimate of the sample size should be based upon sound estimates of the event rate and the usual statistical considerations.

Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations. A relative risk reduction of 30% is acceptable for the power calculations. As there is no way to derive an assured event rate, the study must be event-driven; you must recruit until, based on the observed overall event rate, enough patients are enrolled to achieve the targeted number of events.

A full statistical analysis plan, including detailed plans for handling missing data, must be acceptable to the Division prior to first planned interim analysis.

EXTRAORDINARY RESULTS

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected, useful results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

RECRUITING

Both the dose ranging and the efficacy/safety studies should be performed in patients of both sexes in the pediatric age groups above, approximately evenly distributed among the relevant pediatric age groups to the extent possible given the patient population. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.

DRUG INFORMATION

Use an age-appropriate formulation in the effectiveness study described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

GENERAL CONSIDERATIONS

Labeling that may result from the study(ies): Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies.

Format of reports to be submitted: You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and

referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/cder/guidance/6766fnl.pdf.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before July 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission, "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission, "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to:

Director, Office of Generic Drugs
HFD-600
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (*i.e.,* approval, approvable, not approvable); or

4. the exclusivity determination (*i.e.*, granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked, "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov and http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank.

Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
301.796.1130

Sincerely,

{See appended electronic signature page}

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

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/s/

Robert Temple
8/24/2007 05:44:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 34,663

Sanofi-Aventis
Attention: Marjorie Christie, Ph.D.
Director, Regulatory Development
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Dr. Christie:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also refer to your May 9, 2006, request, serial number 631, for a special clinical protocol assessment, received May 10, 2006. The protocol is entitled, "International Randomized Double-Blind Study Evaluating the Efficacy and Safety of Clopidogrel 0.2 mg/kg Once Daily Versus Placebo in Neonates and Infants with Cyanotic Congenital Heart Disease Palliated with a Systemic- to- Pulmonary artery Shunt (*e.g.* Modified Blalock-Taussig Shunt)."

We have completed our review of your submission and, based on the information submitted, have the following comments:

Clinical:

1. Handling of missing data is not optimal. Sensitivity analyses assigning worst case scenario to withdrawals and loss to follow-up cases is to be considered.

2. The bidirectional Glenn shunt procedure before month four of age should not be considered a component of the primary endpoint for the following reasons:

   - Most of the published hypotheses/conclusions were based on small numbers of cases.

   - The risk of younger age < 120 days was never studied prospectively. It was always determined by post-hoc analyses.

   - Other more important determinants of the outcome, including the extent of the anatomic anomaly, mean pulmonary pressure and the presence of arrhythmia, are factors that necessitate the conduct of such surgery at an earlier age, and therefore would confound the evaluation of the study drug.

   - Need for stage II palliative repair and use of the bidirectional Glenn shunt at younger age does not always result from thrombosis that could be affected by the study drug.

   - Only a very small fraction of deaths post stage I palliative repair was due to anoxia (maybe thrombosis).

Statistical:

1. Without further information, it is impossible to know whether the overall type I error is controlled in the proposed interim analyses and the overall power is achieved. More information on interim analyses needs to be provided in order to answer the following questions:

    a. What are the stopping values for futility and efficacy in the second and third interim analyses?
    b. Is the efficacy boundary affected by the futility boundary?
    c. What spending function did you use in calculating the efficacy boundary?
    d. What test statistic is used in the interim analyses?

2. We discourage you from stopping the trial for futility. If the trial is stopped early for futility, the results may not be interpretable.

3. The Data Monitoring Board charter should be submitted for the Division's review.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management, 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
6/16/2006 09:49:29 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 34,663 / NDA 20-839

sanofi-aventis U.S., Inc.
ATTENTION: Colleen M. Davenport, Ph.D.
Director, Regulatory Development
9 Great Valley Parkway
PO Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for clopidogrel bisulfate (SR25990C).

We also refer to your amendment dated April 10, 2008, providing the Statistical Analysis Plan for protocol EFC5314, "International, randomized, double-blind, clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic - to – pulmonary artery shunt (e.g. modified Blalock-Taussig shunt)." This study is being conducted in response to our Pediatric Written Request.

We have the following comments and recommendations:

Regarding the interim analysis, the information you provided is not sufficient to confirm your calculation for efficacy and futility boundaries. We remind you that the efficacy boundaries should not be affected by the futility boundaries. That is, the efficacy boundaries should be generated, assuming that there are no futility boundaries. Furthermore, given (as you stated in the amendment) that there was only limited knowledge of the use of this drug in this patient population and that the variability of the estimated treatment effect could be much larger (earlier interim data analysis finding) than was observed in the later interim analyses, it is a better strategy to use much less alpha for early interim analyses and leave most of the alpha for the final analysis. Thus, we strongly recommend that you choose a conservative spending function (e.g., O'Brien and Fleming type of alpha spending function). Finally, we found that the estimates that you used to determine the required number of events [i.e., "30% relative reduction" for the primary event rate (28% rate in the test group)] seem overly optimistic, especially for a study that will be used to seek pediatric exclusivity. Please provide us with a detailed justification regarding the use of these assumptions (i.e., 30% reduction and 28% rate).

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug

that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

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

Sincerely,

{See appended electronic signature page}

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

Linked Applications	Sponsor Name	Drug Name
IND 34663	SANOFI-AVENTIS U S INC	PLAVIX (CLOPIDOGREL BISULFATE SR)TABS

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

/s/

NORMAN L STOCKBRIDGE
05/09/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 34,663

sanofi-aventis U.S., Inc.
ATTENTION: Colleen M. Davenport, Ph.D.
Director, Regulatory Development
9 Great Valley Parkway
PO Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

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

We also refer to your amendment dated August 27, 2008, containing an amended Statistical Analysis Plan (SAP) for protocol EFC5314 entitled, "International randomized double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic- to- pulmonary artery shunt (e.g. modified Blalock Taussig shunt)."

We have completed our review and find the above reference submission acceptable. Although we still would like you to consider a more stringent stopping boundary for efficacy as noted in our teleconference on July 31, 2008, the stopping boundary contained in the August 27th submission is indeed statistically valid. We have no further comments at this time.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

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

Linked Applications	Sponsor Name	Drug Name
IND 34663	SANOFI-AVENTIS U S INC	PLAVIX (CLOPIDOGREL BISULFATE SR)TABS

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/s/

NORMAN L STOCKBRIDGE
09/03/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 34,663

ADVICE/INFORMATION REQUEST

sanofi-aventis U.S., Inc.
ATTENTION: Colleen M. Davenport, Ph.D.
Director, Regulatory Development
9 Great Valley Parkway
PO Box 3026
Malvern, PA 19355

Dear Dr. Davenport:

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

We also refer to your amendment dated December 1, 2009, containing your request for Agency feedback regarding specific sections of your July 2010 fulfillment of a Pediatric Written Request.

Upon review of the above mentioned document, we would like you to consider the following comments:

1) We believe that studies in adult baboons may not be adequate to explore PK/PD and to predict toxicity in a pediatric population. The Guidance for Industry: "Nonclinical Safety Evaluation of Pediatric Drug Products " dated February 2006 states that in the following circumstances juvenile animal studies are not necessary:

   - Data from similar therapeutics in a class have identified a particular hazard and additional data are unlikely to change this perspective;
   - There are adequate clinical data because adverse events of concern have not been observed during pediatric clinical use; or
   - Target organ toxicity would not be expected to differ in sensitivity between adult and pediatric patients because the target organ of toxicity is functionally mature in the intended pediatric population and younger children with functionally immature tissue are not expected to receive the drug.

   Please provide a rationale with supportive data if you believe one or more of these circumstances are applicable and therefore studies in juvenile animals are not required. The absence of pre-clinical safety studies in juvenile animals may be a review issue.

2) We also agree with your proposal to include the Case Report Forms and datasets as detailed under question 2 of the December 1, 2009 submission. Please also include in the dossier not only those narratives and CRFs for subjects who discontinued due to an adverse event, but rather for all subjects who discontinued regardless of reason.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those

responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-34663	GI-1	SANOFI-AVENTIS U S INC	PLAVIX (CLOPIDOGREL BISULFATE SR)TABS

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

/s/

ALISON L BLAUS
03/08/2010

NORMAN L STOCKBRIDGE
03/08/2010

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

Transmitted via email:	Colleen.Davenport@sanofi-aventis.com
Attention:	Colleen Davenport
Company Name:	sanofi aventis
Phone:	610-889-8556
Subject:	**IND 34,663 – 10May10 Pediatric sNDA Meeting Minutes**
Date:	26 May 2010
Pages including this sheet:	18
From:	**Alison Blaus**
Phone:	**301-796-1138**
Fax:	**301-796-9838**

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date:	10 May 2010
Application:	IND 34,663
Drug:	clopidogrel bisulfate
Sponsor:	sanofi aventis
Meeting Purpose:	Pediatric pre-sNDA
Meeting Type:	Type B

FDA Participants:

**Office of Drug Evaluation I*	
Robert Temple, M.D.	Director
** Division of Cardiovascular & Renal Drugs*	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Martin Rose, M.D., JD	Medical Officer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Muriel Saulnier, Ph. D.	Pharmacologist
Edward Fromm, RPh, RAC	Chief Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager
** Pediatric and Maternal Health Staff (PMHS)*	
Hari Cheryl Sachs, M.D.	Team Leader, Medical Officer
Virginia Elgin, M.D.	Medical Officer
** Division of Biometrics I*	
Yeh-Fong Chen, Ph.D.	Mathematical Statistician
** Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D	Team Leader, Clinical Pharmacology
Elena Mishina, Ph.D.	Clinical Pharmacology
** Electronic Submissions*	
Valerie Gooding	Electronic Submission Support Staff

sanofi aventis Participants:

Richard Gural, Ph.D.	Global Regulatory Affairs
Colleen Davenport, Ph.D.	Global Regulatory Affairs
Nancy Kribbs, Ph.D.	Global Regulatory Affairs
Weiya Zhang, Ph.D.	Global Biostatistics
Catherine Marchese, M.D.	Global Clinical Development
Sylvie Fontecave, M.D.	Global Clinical Development
Ghislaine Pisapia, M.Sc.	Global Research and Development

Bristol-Myers Squibb Participants:

Anthony Waclawski, Ph.D.	Global Regulatory Science
Melvin Blumenthal, M.D.	Global Clinical Research
Ronald Portman, M.D.	Global Clinical Research
Mark Sumeray, M.D.	Global Medical Affairs
Phil Hornick, M.D.	Global Medical Affairs
Andres Gomez, Ph.D.	Epidemiology

Background:
Clopidogrel is a P2Y12 inhibitor currently marketed for treatment of patients with acute coronary syndrome (ACS) and those with recent MI, recent stroke, or established peripheral arterial disease. The clopidogrel pediatric developmental program was initiated in 2000 to determine if administration of clopidogrel to infants who have undergone systemic-to-pulmonary artery shunt placement for congenital heart disease would prevent shunt thrombosis. After meeting with the Division regarding formulation, dosing, appropriate patient population, and trial design, the sponsor submitted a proposed pediatric study request. The Agency responded with a Pediatric Written Request (PWR) on October 15, 2001. After completion of a dose-ranging study in children (PICOLO), the sponsor met with the Division to discuss their planned special protocol assessment (SPA) for the Phase 3 safety and efficacy study (CLARINET). This SPA was submitted on May 9, 2006 and the Division responded with a No Agreement letter on July 12, 2006. Subsequently, the PWR was amended, dated August 24, 2007, to reflect the agreements. After CLARINET was initiated, there were a number of revisions to the statistical analysis plan in response to Agency advice (letters dated May 9, 2008, September 3, 2008 and a teleconference on July 31, 2008).

This purpose of this sNDA meeting is to present the results from the CLARINET study, discuss the implications of these results, and to discuss the format and content of their planned pediatric sNDA. The sponsor is planning on submitting their sNDA on July 15, 2010.

Questions for the Division:

1. Does the Agency agree with the content of the proposed supplemental NDA (as detailed in Appendix B of the briefing book)?

   FDA Preliminary Response:
   Yes, the Agency agrees with the proposed eCTD structure for the planned sNDA. We have the following comments and requests from the ESUB group:

   - Please include in the cover letter the technical point of contact information (i.e. tel/fax nos. and email address)
   - Provide a linked **reviewer's aid or reviewer's guide in module 1 as a separate document from the** cover letter to ease locating information in the application
   - Please provide sufficient navigation (bookmarks, hyperlinks, TOCs)
   - Submit Section 5.2 as a single pdf file with links to the clinical studies in Module 5

   For Study EFC5314, in addition to your final analysis results, please include your original interim analysis plan and interim analysis results in the NDA submission. Please note that the interim analysis plan should include the planned standard operating procedures, and the interim analysis results should include the DMC meeting minutes and decisions.

   Discussion During Meeting:
   As noted in the slides, attached as an Appendix to these minutes, the sponsor agreed to all the requests in the preliminary comments above. The Division agreed with the sponsor that only minimal information about the formulation used in CLARINET needs to be submitted in Module 3 of the sNDA because there are no plans to market the formulation utilized in the pediatric studies.

2. Does the Agency agree with the proposed plan to modify the labeling? Following the results of the CLARINET study, the Sponsor is planning to update Section 8.4 (Use in Specific Populations-Pediatric Use) of the labeling with information related to safety and efficacy from the CLARINET study.

FDA Preliminary Response:
The Division did not receive the complete proposed label.

Discussion During Meeting:
Proposed wording was provided to the Division in the attached slides, but the Division reserved comment until the formal review of the sNDA.

The sponsor did highlight that they did not plan revisions to the pharmacodynamic section of the labeling, which Dr. Stockbridge agreed was appropriate.

3. **Is the sponsor's proposal for inclusion of narrative**s, CRFs, and datasets acceptable to the Agency?

FDA Preliminary Response:
Yes.

Discussion During Meeting:
No further discussion on this topic.

4. Would the Agency confirm the process for the review of the sNDA, compliance with the PWR and the determination of exclusivity extension?

FDA Preliminary Response:
The decision regarding the granting of exclusivity will be made by the Exclusivity Board and is based on meeting the terms of the WR once the studies are submitted and an exclusivity determination requested. In order for both the Agency and the Sponsor to help determine compliance with the PWR, consider submitting an annotated PWR that charts what is required in the PWR compared to the studies that have been completed (PICOLO and CLARINET) and where in the application it can be found, a summary of available data on the use of clopidogrel in patients undergoing systemic-to-pulmonary artery shunt placement, as well as the safety information outlined in the WR, including:

- Safety data from single center registries at Boston MA and Leuven Belgium
- Safety data from two U.S. claims databases (Ingenix Research and Premier Healthcare)
- A summary of spontaneous adverse event reporting linked to off-label use of clopidogrel in children from your post-marketing pharmacovigilance database
- An analysis of the available published literature on the use of clopidogrel in pediatric patients.

We intend to make the determination within 90 days after submission of the sNDA since Written Requests issued prior to FDAAA 2007 are reviewed under pre-FDAAA timelines.

Discussion During Meeting:
The sponsor agreed to provide an annotated PWR documenting the contents of the sNDA relative to the items requested as part of the PWR. They also mentioned that they would include the complete study report and any data from available on shunt patients.

The Division asked about the doses administered in the single center registries. Sanofi stated that a range of doses was administered. The Division said that there was interest in outcomes after higher doses than those administered in CLARINET because the dose administered in CLARINET may have been too small. Sanofi said that the dose used was based on the data from PICOLO indicating the dose administered in CLARINET was one that resulted in 30-50% inhibition of platelet aggregation. The Division pointed out that the dose administered in CLARINET was only about 20% of the adult dose on a mg/kg basis and that there is no obvious reason for there to be such a

large difference in dose requirements. It also noted that the dose was the highest dose explored in PICOLO and so the sponsor has no data about the effects of a higher dose. Finally, it noted that the incidence of bleeding in subjects in CLARINET given clopidogrel was the same as the incidence in placebo patients, an unlikely outcome if drug administration had resulted in significant inhibition of platelet aggregation. The Division stated that unless the sponsor provides additional data, the possibility that an ineffective dose was used in CLARINET should be described in the label so that the trial will not be viewed as conclusively demonstrating that P2Y12 inhibition is ineffective in reducing the incidence of shunt thrombosis in children with systemic-to-pulmonary artery shunts.

Dr. Rose requested that the safety data from the published literature described above be provided to the Division in an organized and systematic manner. The sponsor agreed to provide an outline, including a TOC, of what they plan to include in the submission and its organization.

FDA Additional Requests:

1. Please provide the datasets relating clopidogrel dose to inhibition of platelet aggregation from PICOLO. Please provide an analysis of the clopidogrel dose response relationship based on those data.

   Discussion During Meeting:
   The sponsor agreed to comply with the above request.

2. Please provide the pharmacodynamic data on the inhibition of platelet aggregation from CLARINET electronically.

   Discussion During Meeting:
   The sponsor agreed to comply with the above request.

3. Please provide the following additional information about the time between shunt placement and randomization and between shunt placement and the first dose of study drug in CLARINET at our upcoming meeting on May 10, 2010:
   - Tables and a listing of data relating to (a) the number of days between shunt palliation (i.e., shunt placement) and the date of randomization, and (b) the number of days between shunt placement and the date of the first dose of study treatment, both as a function of calendar time during the study. A multi-tabbed Excel spreadsheet was sent via email on May 3, 2010 to Colleen Davenport, which describes the data we would like to see.
   - Tables showing the primary study outcome and its components (similar in content to Tables 10 **and 12, respectively, in the "Key Results Memo" for EFC5314 that was provided in your** briefing package of April 9, 2010) for each of the four subsets of patients in CLARINET that **are described under the table subheading "Weeks from shunt palliation to randomization" in Table 4 – Summary of initial shunt palliation of the "Key Results Memo" in your briefing** package on page 16. For example, there should be a table similar in content Table 10 and another table similar in content to Table **12 for the subgroup of patients with "≤ 1 week"** between shunt palliation and randomization, and similar tables for each of the other 3 subsets of patients defined by the time from shunt palliation to randomization.

   If this information cannot be provided to us at the meeting on May 10, please send it to us as soon a possible after the meeting, and also include it in your planned NDA supplement.

   Discussion During Meeting:
   Sanofi agreed that although the PWR and protocol instructed that all patients should be randomized as soon as possible after shunt placement, the randomization was delayed in most cases. They explained that the delay occurred because physicians wait until they felt the patients were clinically

stable before enrolling them. The sponsor has reviewed the date of randomization relative to outcome and did not see an interaction. The Division felt that unless the sponsor has definitive data that the delay in initiating therapy had no effects on outcomes, the delay should be noted in the description of the study in the label again so that the trial will not be viewed as conclusively demonstrating that P2Y12 inhibition is ineffective in reducing the incidence of shunt thrombosis in children with systemic-to-pulmonary artery shunt.

Dr. Rose confirmed with the sponsor that they will include the age at randomization in the data included in the sNDA.

Additional Discussion Topics at Meeting:
Dr. Mishina asked the sponsor whether they found any correlation between their clinical outcome and pharmacodynamics. The sponsor explained that they thought thrombosis was associated, but they were unsure about the degree of association.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Robert Temple, M.D.

Draft: ab 13May10
Final: ab 26May10

RD:
Mishina 13May10
Madabushi 13May10
Ventura 14May10
Chen 14May10
Elgin 21May10
Sachs 21May10
Rose 21May10
Grant 24May10
Stockbridge 25May10
Temple 25May10

PLAVIX® (clopidogrel bisulphate) Pediatric Written Request Program

May 10, 2010 Pre-sNDA Meeting

Pediatric Program Summary

- PWR agreed to with Agency in October 2001; last amended August 2007
- Comprehensive pediatric program started in 2000
  - Phase 2 pharmacodynamic dose-ranging trial (PICOLO)
    - Established dose for Phase 3
  - Phase 3 placebo-controlled, event-driven efficacy trial (CLARINET) in 906 patients from 31 countries (178 US patients)
  - Comprehensive summary of safety
  - Specific formulation developed for neonates and infants
    - Powder to be constituted in solvent for oral solution
    - Bioavailability study (solution vs. tablet)
- A proposed update to the label reflecting this pediatric information is planned
- All aspects of the PWR have been addressed

FDA Response from May 6, 2010

Question 1

- **Agency agreed to proposed eCTD structure for planned sNDA**
  - Technical comments will be applied
  - Required information related to interim analyses will be provided
  - Module 3 and Module 4 will not be included in the eCTD
    - A commercial formulation was developed, but due to the results of the CLARINET study and the recommendation not to use clopidogrel in children, Module 3 is not included in the dossier
  - eCTD submission is planned for July 15, 2010

Question 2
Proposal of labeling modifications (1/2)

(b) (4)

Question 2
Proposal for labeling modifications (2/2)

(b) (4)

FDA Response from May 6, 2010

Question 3

- The Sponsor will provide the narratives, CRFs and datasets as requested.

Response to Question 4

- An annotated PWR will be provided

- The safety information in response to point 3 of the PWR will be composed of the following:

  - Safety data from the clinical program of PICOLO and CLARINET
  - A summary of spontaneous adverse event reporting linked to off-label use of clopidogrel in children
  - Published data on the safety of Plavix in pediatric populations worldwide
  - Publication and reports of safety data from two single center registries (Boston, MA and Leuven Belgium)
  - A report including safety data from inpatient (Premier Research Database) and outpatient (Ingenix Research Database) databases

- Does the Agency concur that the above safety information will satisfy the PWR?

Additional Requests 1, 2 and 3

1 - The Sponsor will provide the datasets relating clopidogrel dose to platelet aggregation from PICOLO, and the analysis of the clopidogrel dose response relationship in the sNDA.

2 - As reflected in the amended PWR (August 24, 2007), the requirement for the collection of PD data as part of the CLARINET study was removed

3 - Data concerning the primary study outcome and its components [in relation to the time between shunt placement and randomization and between shunt placement and first dose of study drug in CLARINET] was emailed to Alison Blaus on May 6, 2010 and formally submitted to the IND on May 7, 2010; Sequence #0914. This information will also be included in the CLARINET Clinical Study Report, which will be included in the sNDA.

Summary

- An extensive pediatric clinical development plan was undertaken lasting approximately 10 years
- The benefit in the studied pediatric population was not established
- Appropriate revisions to the labeling will be proposed
- Response to the PWR will be fully annotated demonstrating full compliance with the request

Backup Slides

Point 3 of August 2007 PWR – Amendment 1

- "Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing systemic to pulmonary artery shunt placement as well as a comprehensive safety evaluation of clopidogrel use in children. The safety evaluation in children receiving clopidogrel must include more than a summary of the published literature and include formal analyses of the available published and unpublished safety information. Examples of sources for unpublished safety information include institutions or organizations that systematically collect such data as part of their healthcare delivery to pediatric populations"

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-34663	GI-1	SANOFI-AVENTIS U S INC	CLOPIDOGREL BISULFATE

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

/s/

ALISON L BLAUS
05/26/2010

ROBERT TEMPLE
05/26/2010

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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FDA
10903 New Hampshire Ave
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Transmitted via email:	Colleen.Davenport@sanofi-aventis.com
Attention:	Colleen Davenport
Company Name:	**sanofi-aventis**
Phone:	**(610) 889-8556**
Subject:	**IND 34,663 (NDA# 20-839) clopidogrel Pediatrics SAP Teleconference**
Date:	20 August 2008
Pages including this sheet:	7
From:	**Alison Blaus**
Phone:	**301-796-1138**
Fax:	**301-796-9838**

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Minutes of a Teleconference Between Sanofi-Aventis and the FDA Division of Cardiovascular and Renal Products

Sponsor:	Sanofi-Aventis / Bristol-Myers Squibb
Drug:	Plavix (clopidogrel) Tablets
IND:	34,663 (NDA #20-839)
Date of FDA request:	14 July 2008
Date request received:	14 July 2008
Date of Sanofi-Aventis confirmation:	24 July 2008
Date of meeting:	31 July 2008
Time:	3:30 – 4:30pm
Type/Classification:	Type C; Guidance
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting recorder:	Alison Blaus

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products
Salma Lemtouni, M.D.	Medical Officer
James Hung, Ph.D.	Director, Division of Biometrics I
John Lawrence, Ph.D.	Statistician
Jialu Zhang, Ph.D.	Statistician
Yeh-Fong Chen, Ph.D.	Statistician
Alison Blaus	Regulatory Health Project Manager

Sanofi-Aventis Participants:

Regulatory:	Colleen Davenport, Ph.D.
	Nancy Kribbs, Ph.D.
	Jon Villaume, Ph.D.
Clinical:	Christophe Gaudin, M.D.
	Sylvie Fontecave, M.D.
Biostatistics:	Deborah Dukovic, MA.S.
	Alexander Boddy, M.S.
Project Direction:	Ghislaine Pisapia, M.Sc.

Bristol-Myers Squibb:

Regulatory:	Nic Scalforatto, D.V.M.
Clinical:	Amit Rakhit, M.D.
Biostatistics:	Anne Pieters, Ph.D.

Background:

In response to an updated Statistical Analysis Plan (SAP) regarding the Pediatric Written Request study CLARINET, the Division responded with an Advice Letter, dated May 9, 2008. The letter detailed our three main statistical concerns regarding this amendment. The first concern was that the efficacy boundaries were affected by the futility boundaries instead of being independent of each other. Second, we recommended that a conservative alpha spending function was chosen (e.g., O'Brien and Fleming). Lastly, we believed that the proposed relative risk reduction rate of 30% was overly optimistic and that further justification for these

values was requested. In response, the sponsor maintained that all aspects of their SAP were per prior agreements with the Agency and more specifically, the Pediatric Written Request. The sponsor insisted on using the earlier proposed boundaries for the interim analysis, where the type I error rate was not controlled at a 0.05 significance level if the sponsor does not stop the trial when the futility boundary is crossed. The Agency requested a meeting with the sponsor to discuss these issues; While these were issues to discuss, the interim analysis plan needed discussion as a whole. Since the sponsor's trial was for the purpose of exclusivity, we advised them to make a plan to follow the patients even though the trial is stopped for futility. Of note, after the above message was conveyed to the sponsor, the sponsor sent an email to the Agency project manager prior to this meeting. The email included revised interim efficacy boundaries which were calculated independently, i.e., not binding with the futility boundaries. This email is attached to the meeting minutes as a reference.

Discussion:

The sponsor has recalculated the efficacy boundaries, which were not binded with futility boundaries per the Agency's request and the Agency expressed that the proposed boundaries were confirmed. The whole discussion was mainly about the futility boundaries.

Dr. Stockbridge reinforced that although this study was powered to detect a relative risk reduction of 30% per the Written Request, we would care about an effect smaller than that if the trial is stopped for futility. To ensure that the trial will not be stopped with a meaningful effect size, the sponsor was asked to compute an independent confidence interval for the observed effect size at the interim look. In order to stop for futility, the upper bound of this confidence interval should rule out 30% treatment effect and the percentage of coverage of the confidence intervals should be calculated based on the 0.05 significance level. The sponsor expressed the difficulty of this approach. The confidence interval could be very wide. In addition, the sponsor was concerned that if the trial crossed the futility boundary, they would have a hard time continuing the trial with the DMC approval. The sponsor maintained that meeting the 25% mark would be sufficient to show no treatment effect. It was agreed that if the DMC stopped the trial due to safety concerns that it would be grounds for reproach with the FDA and that the Division will most likely agree with the DMC's call for stopping the trial.

The Agency recommended that Sanofi Aventis/ Bristol-Myers Squibb do the following:

1. The sponsor is to provide boundaries for this trial where the futility is not bound to efficacy and that they are truly independent of each other.
2. The sponsor committed to talking to the DMC and discussing with them whether the FDA's suggestions were acceptable.
3. The sponsor did not agree to a less than 30% relative risk reduction in order to determine that the trial was ineffective. They will meet internally to propose another course of action which may/may not be agreeable with the Division.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Norman Stockbridge, M.D., Ph.D.

Draft: ab 8/8/08
Final: ab 8/20/08

IND 34,663 (NDA#20-839) Pediatrics SAP Teleconference

RD:

Chen 8/8/08
Zhang 8/13/08
Lawrence 8/14/08
Hung 8/15/08
Stockbridge 8/19/08

Blaus, Alison

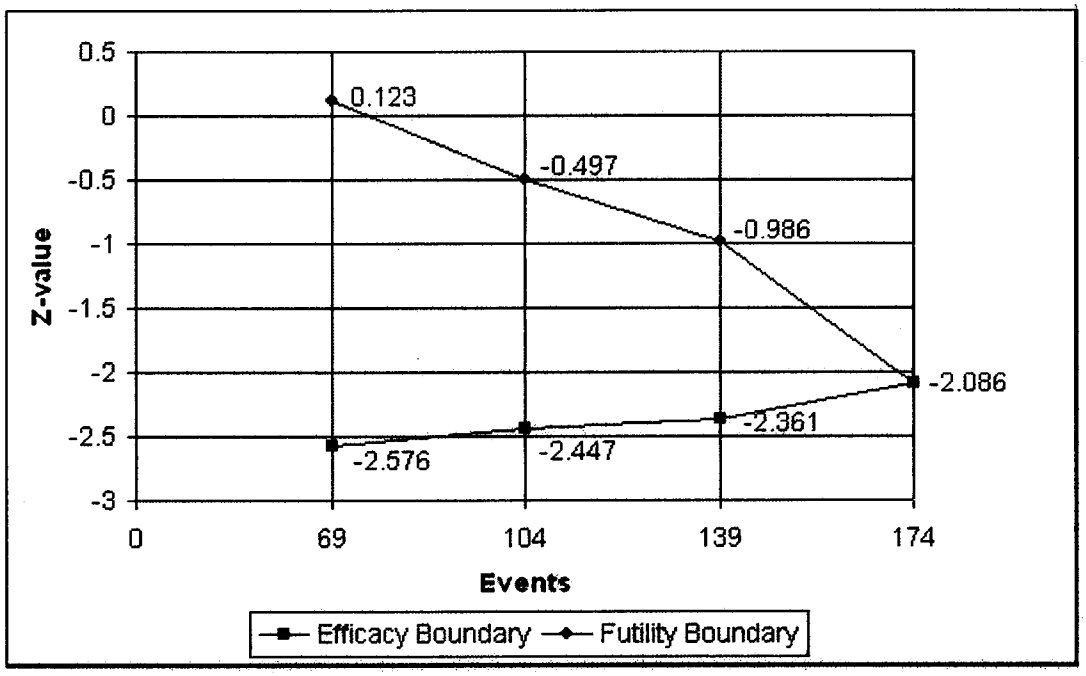
From: Colleen.Davenport@sanofi-aventis.com
Sent: Monday, July 21, 2008 11:11 AM
To: Blaus, Alison
Subject: Clopidogrel (IND 34,663 / NDA 20-839) Pediatrics SAP Meeting

Dear Alison,

In order to maintain the 22 July 2008 scheduled DMC meeting for the 1st interim analysis, we will agree to the FDA comment in the 9 May 2008 Advice Letter that the efficacy boundaries not be affected by the futility boundaries, i.e., the efficacy boundaries will be generated assuming that there are no futility boundaries. These revised boundaries will replace the boundaries currently in the SAP, and numbers and text will be updated according. These new boundaries will then be the boundaries used for all interim analyses and the final analysis.

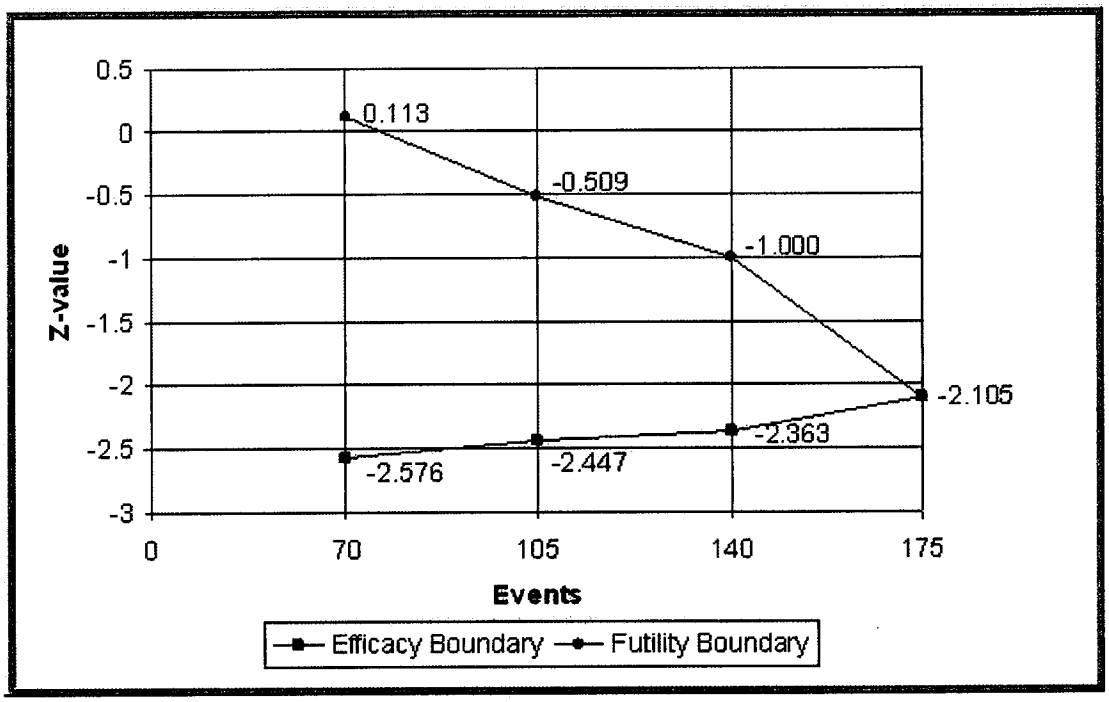
The boundaries in the CLARINET protocol and current proposed SAP are displayed in Figure 1 below. Here, as previously indicated, the type I and II errors are computed considering both boundaries simultaneously.

Figure 1 - Efficacy and futility stopping boundaries (CLARINET protocol)



The boundaries have been recalculated such that the futility boundary is "non-binding" and the efficacy boundary is untouched by the futility boundary. The revised figure is provided below:

Figure 2 – Revised efficacy and futility stopping boundaries (non-binding futility boundary revised 18-Jul-2008))



As can be seen by comparing the two figures, the change is quite minimal, but we will provide these new boundaries to the DMC independent statistical group and the DMC prior to the July 22 meeting so that these boundaries can be applied throughout the study.

Furthermore, as already stated in the SAP, we would not stop the CLARINET study without first consulting the Agency.

> "If applicable, the initial recommendation for early termination of the study would be made by the DMC. The final decision to terminate the study would be made by the Steering Committee, based on the DMC recommendation and after consultation with the FDA."

We are hopeful this answer will be satisfactory to address your request.

Sincerely,
Colleen

Linked Applications	Sponsor Name	Drug Name
IND 34663	SANOFI-AVENTIS U S INC	PLAVIX (CLOPIDOGREL BISULFATE SR)TABS

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

/s/

NORMAN L STOCKBRIDGE
08/20/2008

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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

Transmitted via e-mail to:	**Marjorie Christie, Ph.D.**
Sponsor:	**Sanofi-Aventis**
Phone:	**(610) 889-6852**
Subject:	**Minutes from a Meeting** **End of Phase 2 (pediatric)** **IND 34,663 (7.12.06)**
Date:	August 4, 2006
Pages including this sheet:	8

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

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

End of Phase 2 Meeting with Sanofi-Aventis

Application Number:	IND 34,663
Sponsor:	Sanofi-Aventis
Drug:	Plavix (clopidogrel bisulfate) 75 mg Tablets
Type of Meeting:	End of Phase 2 (Pediatric)
Classification:	Type B
Meeting/Teleconference Date:	July 12, 2006
Preliminary Responses Sent:	July 6, 2006
Briefing Package Received:	June 6, 2006
Confirmation Date:	May 17, 2006
Meeting Request Date:	May 11, 2006
Meeting Chair:	Robert Temple, M.D.
Recorder:	Meg Pease-Fye, M.S.

List of Attendees:

Division of Cardiovascular and Renal Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director
Salma Lemtouni, M.D., M.P.H.	Medical Officer
Patrick Marroum, Ph.D.	Clinical Pharmacology/Biopharmaceutics
Yaning Wang, Ph.D.	
Jialu Zhang, Ph.D.	Statistician
Edward Fromm, R.Ph.	Chief, Project Management Staff
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Sanofi-Aventis:

Lydie Baret-Cormel, M.D.	Regulatory Development
Debbie Dukovic, MA.S.	Biostatistics
Diane Fisher	Regulatory Coordination
Sylvie Fontecave, M.D.	Clinical Development
Christophe Gaudin, M.D.	Clinical Development
Nancy Kribbs, Ph.D.	Regulatory Development
Ghislaine Pisapia, M.Sc.	Project Direction
Jon Villaume, Ph.D.	Regulatory Development
Martin Roessner, M.S.	Biostatistics
Eric Sultan, Ph.D.	Clinical Pharmacology

Bristol Myers-Squibb:

Mel Blumenthal, M.D.	Clinical Research
Amit Rakhit, M.D.	Global Medical Affairs
Nic Scalfarotto, D.V.M.	Regulatory

BACKGROUND

A Pediatric Written Request was sent to Sanofi on October 15, 2001 requesting a proposal for a Phase 3 pediatric protocol. Sanofi performed a dose-ranging study, PICOLO, or "Platelet Aggregation Inhibition in Children On cLOpidogrel: Dose-ranging pharmacodynamic assessment of platelet aggregation inhibition with clopidogrel in children of Blalock-Taussig age categories (neonates and infants/toddlers) in order to determine an appropriate dose. The protocol for PICOLO was submitted on March 18, 2002 (Serial 0368).

Sanofi also established a large multi-center, international registry including over 1000 patients with systemic-to-pulmonary artery shunt for cyanotic congenital disease, in order to document an event rate for the planned primary endpoint (combined incidence of any death, shunt thrombosis requiring intervention and hospitalization for bi-directional Glenn procedure prior to four months of age).

On February 9, 2006, the Division received a meeting request to discuss Sanofi's proposed pediatric protocol entitled, "International randomized double-blind study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (*e.g.* modified Blalock-Taussig shunt," or CLARINET. CLARINET is a prospective, multi-center, placebo-controlled, parallel group clinical study to determine efficacy and safety of clopidogrel in neonates or infants/toddlers with cyanotic congenital heart disease palliated with any systemic-to-pulmonary artery shunt. Neonates (age less than one month) or infants/toddlers (one to 3 months of age) will be randomized to clopidogrel or placebo preferably as soon as they are hemodynamically stable and able to receive the drug orally or parenterally. Approximately 490 pediatric patients will be treated with clopidogrel, 0.2 mg/kg daily, or placebo until they are 12 months of age or until death, or next surgical procedure for correction of the congenital heart disease, whichever comes first. The primary endpoint will be the first occurrence of any component of the primary composite endpoint of shunt thrombosis requiring intervention (including repeated shunt), any death, and hospitalization for bi-directional Glenn procedure or any surgical repair prior to 4 months of age. Blood samples will be obtained from selected centers in a sufficient number of patients (sparse sampling methodology will be used) to analyze the population pharmacokinetic and pharmacodynamic profile of the chosen dose, 0.2 mg/kg, of clopidogrel. Pharmacokinetics will be evaluated based on measurement of the inactive metabolite of clopidogrel using a validated assay.

The original date for this meeting to be held was March 27, 2006 and preliminary responses were sent to Sanofi on March 24, 2006. Because they believed they received sufficient guidance from these initial responses to revise their protocol, Sanofi cancelled the March meeting and requested another meeting on May 1, 2006 and also submitted a Special Protocol Assessment for their pediatric protocol (S-631) on May 10, 2006. The Division sent their SPA comments to Sanofi on June 16, 2006. After receiving the SPA comments, Sanofi noted inconsistencies between the SPA response and the Written Request. Preliminary responses to the submitted briefing package were sent to the sponsor on July 6, 2006 and are reproduced below in *italics.*

1. Does the Division agree that the pharmacodynamic findings in neonates and infants/toddlers are comparable to that in adults and that no additiona1 PD studies are required m the three other pediatric age groups?

Preliminary Response:
We believe you have adequately identified a dose of clopidogrel in neonates and toddlers that achieves about 50% inhibition of ADP-induced platelet aggregation.

We ask that you give a response to the following questions:

- *What is the level of platelet aggregation achieved with 5 micrograms of ADP as a function of age (neonates to adults)?*

- *It appears that the target dose of clopidogrel would be about 0.2 mg/kg in neonates, while it is about 1 mg/kg in adults. How do you propose to justify dose selection for children of intermediate age?*

MEETING

After introductions, Sanofi explained the background of the pediatric protocol and written request. They wanted to discuss the following topics at this meeting:

- The current status of the written request
- The recommended changes made by the Division:
  - Event-driven trial
  - Removal of early Bidirectional Glenn as a component of the primary endpoint
  - Addition of PK/PD measurements
- Clarification of the need to study other age groups (platelet aggregation as a function of age)

Futility

The Division expressed concern about the possibility of stopping the trial if it were deemed unlikely to show a 30% treatment effect, since we would care about an effect smaller than that. Dr. Temple suggested that Sanofi determine the implications of having the study rule out a 15-20% effect size.

Sanofi commented that futility analysis should not be numeric, but that other factors will be weighed by the DSMB (primary endpoints, components of primary endpoints). Dr. Stockbridge agreed, noting that if Sanofi's DSMB stopped the study because of safety, there would still be an answer to the outstanding question; if the Agency is sure that the Written Request has results in an answer about pediatric use, it could revise the Written Request.

Dr. Zhang noted that there are three planned interim analyses in the SPA and noted that not all the critical values have been provided. Sanofi stated that these will be submitted. Dr. Zhang also asked if the effect boundary depends on the futility boundary, and Sanofi noted that they are calculated together.

Use of bi-directional Glenn (BDG) procedure as a component of the primary endpoint

The primary endpoint in CLARINET is any death, shunt thrombosis requiring intervention, and hospitalization for bidirectional Glenn Procedure (BDG). Dr. Stockbridge questioned whether BDG should be included, since there might be reasons for early use of BDG that were unrelated to the patency of the shunt, and the additional events would not help ascertain the drug effect. He also said that the Agency wants only the BDG procedures resulting from shunt thrombosis to be counted, and that those related to other factors (arrhythmias) not counted. Further, he suggested forming a blinded adjudication procedure to determine BDG procedures secondary to a thrombotic event. Dr. Temple suggested that if angiography were used to diagnose the cause of these cases, such adjudication could be waived because the presence of thrombosis could be objectively determined.

Dr. Unger stated that there must be clinical signs that a stent has clotted and asked if the case report form will be designed to capture these symptoms and signs. Sanofi replied that it will. The Division still

emphasized the need of the use of an adjudication committee. Sanofi responded by saying that they do not want to make their study more complicated than it already is, and that it is difficult to distinguish shunt-thrombosis-related events in this type of secondary stage repair. Dr. Lemtouni agreed, adding that this is why it is important to collect as much information as can be captured in the CRF. Dr. Unger added that there should be clear criteria for decisions regarding the presence or absence of shunt thrombosis.

PK/PD Sub-studies

Dr. Stockbridge said that since PK-PD sub-studies are not included in the Written Request, Sanofi should take this as advice, not a requirement. Sanofi said they would do their best to obtain what the Division is looking for. There was some internal debate as to the value of either PK or PD, but the Agency requested that when samples are taken, that baseline and treatment samples be obtained from the same subject. Sanofi agreed.

Dose range and study of other age groups

Dr. Stockbridge asked the sponsor to provide data from their platelet inhibition study to show the agonist effect of ADP in neonates. If the response in neonates is similar to that in adults, then the dose range seems reasonable. If it is markedly less than in adults, the premise for the study may need to be reconsidered.

CONCLUSION

All agreed that Sanofi may proceed with the study and that no further review of the protocol is necessary.

ACTION ITEMS

- Sanofi will re-calculate the futility boundaries for an effect size of between 15 and 20% and will submit a new proposal.
- Sanofi will submit details for the proposed interim analyses.
- Sanofi will submit a proposal of how to differentiate between BDG procedures that are thrombosis-related and those that are not.
- Sanofi will provide ADP agonism data for platelets of neonates.

Date Minutes Drafted: July 14, 2006
Date Minutes Finalized:

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

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

Reviewed:
R. Temple
N. Stockbridge 7.24.06
E. Unger 7.21.06

S. Lemtouni	7.20.06
P. Marroum,	7.14.06
J. Zhang	7.14.06
E. Fromm	7.21.06

Attached: slides

Clopidogrel
Pediatric Development Program

End of Phase 2 Meeting
July 12, 2006

Sponsor Attendees

Sanofi-aventis U.S. Inc.
- **Lydie Barst-Cormel, M.D. Regulatory Development**
- **Debbie Dukovic, M.A.S., Biostatistics**
- **Diane Fisher, Regulatory Coordination**
- **Sylvie Fontecave, M.D., Clinical Development**
- **Christophe Gaudin, M.D. Clinical Development**
- **Nancy Kribbs, Ph.D., Regulatory Development**
- **Ghislaine Pisapia, M.Sc., Project Direction**
- **Martin Roessner, MS., Biostatistics**
- **Eric Sultan, Ph.D., Metabolism and Pharmacokinetics**
- **Jon Villaume, Ph.D., Regulatory Development**

Bristol-Myers Squibb
- **Mel Blumenthal, M.D., Clinical Research**
- **Amit Rakhit, M.D., Global Medical Affairs**
- **Nic Scalferotto, D.V.M. Regulatory**

Where We Are

End-of-phase 2 meeting scheduled for March 2006
Background Package submitted: contained proposal for Phase 3 protocol
Based on 2001 Written Request
↓
Preliminary comments on protocol from Division in advance of the meeting
↓ ↓
Sponsor incorporated FDA comments and submitted as SPA ↓ | Meeting dedicated to address other age group requirements ↓
Division comments on SPA received; Not consistent with Written Request ↓ | Background package submitted
↓
Therefore....

Meeting Topics

- Current status of the written request
- Changes suggested by the Division
  - **Event driven trial**
  - **Not consider early Bidirectional Glenn as component of Primary endpoint**
  - **PK/PD measurements**
- Clarify the need to study other age groups
  - **Platelet aggregation as a function of age**
  - **Other age groups and dose recommendation**

Written request and status

Goal: use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunt (eg MBTS) for the palliation of cyanotic congenital heart disease

Pediatric development plan:
- **Find a pediatric formulation (liquid formulation) and conduct a bioavailability study → done**
- **Provide the appropriate dose for an efficacy/safety study with a Steady state PD dose ranging study in pediatric shunt patients who are in the age of MBTS: PICOLO study → done**
- **Collect data to demonstrate a realistic event rate for the Phase III primary endpoint: event log registry of 1004 patients → done**
- **Summarize all the data available on the use of clopidogrel with its safety in children: registries → done and health care DB interrogation → planned**
- **Complete an efficacy and safety placebo-controlled study in patients with any systemic-pulmonary artery shunt → CLARINET study**

Phase III Statistical Considerations

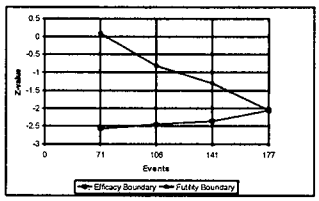
Written Request:
- **"The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations."**
- **"Objective clinical data demonstrating a realistic event rate... at least 80% power... a conventional level of significance (0.05)"**

Based on the above and the registry, the original protocol (March 6th 2006) was to enroll 490 patients

In response to new March 24th request for an event driven trial the revised protocol (May 3rd) includes:
- **177 expected events**
- **Sequential design protecting the type I error with 3 interim analyses and formal stopping rules for overwhelming efficacy and futility**

The division discourages from stopping the trial for futility

CLARINET: Event-driven trial design



***Sequential design with 3 interim analysis at 40, 60 and 80% of the 177 required events**

***Ethical considerations : stopping rules for overwhelming efficacy and futility**

CLARINET: Sequential design

		Conditional Power Calculated under		
Interim Analysis	Observed HR	Current Trend*	Blended Hypothesis**	Original H_1
1st	1.02	< 1%	7%	29%
2nd	0.85	1%	14%	34%
3rd	0.80	2%	11%	25%

*assuming the remaining population will behave like the first patients enrolled
**weighted average of current trend and original H_1, with weight based on proportion of accumulated information

CLARINET primary endpoint

- Primary endpoint as defined in the written request (2001) :
  first occurrence of any component of the primary composite endpoint of:
  - **Any death**
  - **Shunt thrombosis requiring intervention,**
  - **Hospitalization for bidirectional Glenn procedure prior to 4 months of age**

Rationale for bidirectional Glenn procedure prior to 4 months of age:

FDA Meeting Minutes March 28th 2000

- "It is not possible to perform the BDG procedure in neonates due to pulmonary vascular resistance.
- At two to three months , it is possible to perform BDG procedure , although the risk to the patient is still high
- It is optimal if the BDG procedure can be delayed until 4-6 months of age
- If the shunt narrows too quickly and the physician is forced to perform the BDG prematurely the risk to the patient is greatly increased
- The Agency suggested that the Sponsor focus on this factor (acceleration of the surgery schedule) as an endpoint."

- Current published data based on more than 2000 patients show that BDG procedure or any other repair performed prior to 4 months is still associated with an increased mortality
- Most recent data still support the endpoint described in the written request
- Therefore the sponsor requests that the agency agree to maintain "**Hospitalization for bidirectional Glenn procedure or any shunt-related cardiac intervention prior to 4 months of age**"
  as a component of the primary endpoint

CLARINET PK /PD substudies

- Excerpt from written request: « **Blood samples should be obtained in a sufficient number of subjects to analyze PK and PD profile for the chosen dose of clopidogrel, with PK based on the levels of the inactive metabolite of clopidogrel. Sparse samplings methods can be used, provided sufficient samples are obtained at 4 times (one before peak serum concentration, 2 following the peak and one at or around the time of peak concentration)** »
- Protocol proposal:
  - **PK or PD sampling done according to local regulations, only at selected sites and if parents or patient's representative have signed specifics informed consent**
  - **PK substudy**
    Assessment of SR26334 exposure and possible relationship with covariates such as age, weight, height, gender, adverse events and *PD when available.*

Dose	Cmax (h)	Plasma samples for SR26334
[illegible]	[illegible]	[illegible]

  - **Platelet aggregation inhibition will be measured by accredited laboratory personnel at baseline (pre-dose) and at steady-state (on-treatment)**

Biopharm comments (June 22, 2006)

- FDA comments:
  - **The relationship between individual PK exposure and primary efficacy/safety endpoints should be explored.**
  - **If PK/PD (ADP-induced platelet aggregation) relationship will be explored, please collect PK and PD information from the same patients**
  - **If plasma samples are limited, priority should be given to PK**
- Sponsor answers:
  - **The above was not part of the written request**
  - **Only the inactive metabolite is assessable by PK**
  - **The paucity of expected samples makes this impossible**
  - **Therefore, the sponsor suggests retaining the original protocol proposal**

FDA communication received on July 6th regarding the 3 older age groups :

- FDA comments :
  - **What is the level of platelet aggregation achieved with 5 micrograms of ADP as a function of age (neonates to adults)?**
  - **It appears that the target dose of clopidogrel would be about 0.2 mg/kg in neonates, while it is about 1 mg/kg in adults. How do you propose to justify dose selection for children of intermediate age ?**
- Sponsor comments :
  - **These age groups are outside of the scope of the indication mentioned in the written request**
  - **There is no homogeneous population in older age groups where clopidogrel may be used**
  - **The applicability of the previously determined 0.2 mg/kg dose outside of the pulmonary-systemic shunt indication cannot be assessed as not only the age but also the condition may impact on platelet reactivity and inhibition**
  - **Therefore, the sponsor suggests that the evaluation of the 3 older age groups be waived from the written request**

Review of Meeting Topics

- Phase III protocol
  - **Event driven trial / futility**
  - **Early Bidirectional Glenn as component of Primary endpoint**
  - **PK/PD measurements**
- Clarify the need to study other age groups

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

/s/

Margaret Pease-Fye
8/8/2006 08:09:07 AM

Robert Temple
8/8/2006 07:00:24 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs, Ph.D.
Company Name:	Sanofi-Synthelabo Inc.
Phone:	(610) 889-6425
Subject:	meeting minutes
Date:	9/1/00
Pages including this sheet:	7
From:	**Colleen LoCicero**
Phone:	**301-594-5334**
Fax:	**301-594-5494**

Dr. Kribbs,

The minutes from our August 9, 2000 meeting regarding IND 34,663 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

cc: orig IND 34,663
HFD-110
HFD-110/Matthews
HFD-110/LoCicero

Minutes of a meeting

Date:	August 9, 2000
Application:	IND 34,663
Product:	Plavix (clopidogrel) bisulfate Tablets
Sponsor:	Sanofi-Synthelabo Inc.
Purpose:	to further discuss pediatric program
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Colleen LoCicero
Participants:	
FDA	
Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Rachel Behrman, M.D.	Deputy Director, HFD-101
Stephen Fredd, M.D.	Deputy Director, Division of Cardio-Renal Drug Products (HFD-110)
Steven Rodin, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Team Leader, Statistician, Division of Biometrics I (HFD-710)
James Lawrence, Ph.D.	Statistician, HFD-710
Gabriel Robbie, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, Division of Pharmaceutical Evaluation I (HFD-860)
Wendy Chou, Ph.D.	Fellow, Clinical Pharmacology and Biopharmaceutics, HFD-860
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Sanofi-Synthelabo	
Alex Boddy, M.S.	Associate Director, Biostatistics
Jean Bouthier, M.D.	Vice President, Clinical Research
Christophe Gaudin, M.D.	Director, Clinical Research
Richard Gural, Ph.D.	Vice President, Regulatory
Ann Hards, Ph.D.	Director, Regulatory
Nancy Kribbs, Ph.D.	Assistant Director, Regulatory
Bristol-Myers Squibb	
Mel Blumenthal, M.D.	Group Director, Clinical Research
Gregory Torre, Ph.D.	Group Director, Regulatory
Mary Ellen Norvitch, Ph.D.	Director, Regulatory
Consultants	

(b) (4)

[redacted]

Background

The sponsor requested this meeting to further discuss their pediatric program and exclusivity request for clopidogrel. These issues were first discussed at a meeting between the Agency and sponsor in March of this year. The sponsor is proposing to conduct an initial dose ranging study, followed by a study to evaluate the efficacy and safety of clopidogrel in pediatric patients with congenital heart disease who undergo placement of a Blalock-Taussig shunt.

The meeting

Discussion Point #1: Pharmacodynamic dose ranging in older age groups

The Agency will need to address the older pediatric age groups in the Written Request. We would most likely request a population PK/PD assessment in these groups (ADP-induced platelet inhibition).

Discussion Point #2: BSA versus BW

The Agency does not have a preference as to whether dose is expressed in terms of body surface area (BSA) or body weight (as mg/kg). Dr (b) (4) noted that although body weight is probably more frequently used in pediatric dosing, there is no consensus within the pediatric community as to whether one is preferable to the other. Sanofi-Synthelabo does not have a preference either, although they noted that dosing by body weight in a neonatal/infant population might be more physician-friendly. The sponsor's goal for the initial dose-ranging study should be to find a dose that provides blood levels that achieve ~50% platelet inhibition. If a BSA-based normalization is used in the dose-ranging study, it should not be difficult to subsequently convert the selected doses to body weight (mg/kg), if that is the preference. There might be a different correction factor for the conversion from body weight to BSA for different age groups (e.g., the factor for zero to two weeks might differ from that of two to four weeks).

Discussion Point #3: ADP-inhibition test

The sponsor clarified that the platelets used in the platelet inhibition tests are those of the patient.

Discussion Point #4: Background therapy

Currently there is no standard medical therapy for prevention of shunt thrombosis in pediatric patients undergoing placement of a Blalock-Taussig shunt. Heparin is seldom used. Aspirin is used in perhaps 50% of these patients, yet its use is supported by very little data. Many physicians hesitate to use aspirin because of the potential risk of Reye's syndrome.

Sanofi-Synthelabo plans to prohibit the concomitant administration of both aspirin and heparin in the proposed studies. The sponsor does not believe this would deny subjects valuable medical treatment, as aspirin has not been shown to be effective in this setting and is not a standard of care. The Agency was not sure that we would be comfortable with prohibiting investigators from using aspirin, if that is their usual practice. Dr. (b) (4) elieved the use of aspirin in this setting to be primarily determined by the centers and not the individual practitioners. The sponsor therefore could just exclude from participation in the study those centers that routinely use aspirin. The Agency noted that the protocol could leave the decision of whether to use aspirin to the discretion of the investigator, since excluding entire centers might considerably limit enrollment into a study that does not have a large patient population from which to draw.

Additionally, it was noted that permitting the concomitant use of aspirin might decrease the overall effect, which would make detecting a difference between treatments more difficult.

Discussion Point #5: Dose selection for proposed studies

In our first meeting, the Agency recommended that the sponsor study in the dose-ranging study several doses with a 10-fold difference between doses. The sponsor is concerned that this would result in a low dose so low that it has essentially the same effect as placebo and would not provide much information. The sponsor believed they would obtain more useful information from the dose-ranging study if they adjust the margin between doses so that the low dose has at least some effect. The Agency believed Sanofi should start as we had proposed, and, after evaluating for futility the first several patients at the low dose, revise the low dose upward if it appears that it lacks any effect on platelet inhibition. Some concerns with doing this were noted, including the possibility of the same dose, over time, producing a different effect, and the sensitivity of the platelets changing with exposure.

Additionally, the Agency would not recommend that Sanofi study doses that produce levels of exposure higher than what they have previously studied in adults.

Once the dose-ranging study is completed, the sponsor plans to discuss the findings and dose selection for the efficacy study with the Agency prior to proceeding with the efficacy study.

Discussion Point #6: Neonatal age group

Dr. Rodin asked whether the sponsor had considered dividing the neonates into two groups (zero to two weeks and two to four weeks), noting that the CYP P450 isozymes change significantly during the first month. This could result in different dose requirements within the first month.

The sponsor did not believe this would be necessary, as there would be few, if any, patients enrolled into the study prior to two weeks of age. The need for shunt placement is usually not detected in most patients until about five days of age. Surgery is then performed a few days later, and clopidogrel started approximately three days following surgery. Therefore, most patients would not start clopidogrel until close to two weeks of age or older. It would then take seven days for the patient's blood levels to reach steady state. Most patients, therefore, would not be evaluated until one month of age or older. It should be possible, however, for the sponsor to compare those patients started on clopidogrel at three weeks to those started at four.

Discussion Point #7: Patient population

The Agency believed the proposed patient population was acceptable.

Discussion Point #8: Endpoints

The proposed endpoints, total mortality, early bi-directional Glenn procedure (prior to four months of age), and shunt thrombosis requiring intervention, are acceptable to the Agency. Shunt thrombosis would be assessed by clinical auscultation, echo-Doppler, angiography, or surgical or postmortem observation. All death and shunt thrombosis will be counted as events up until the 'Glenn' procedure is performed. 'Glenn' procedures performed after four months of age will not be counted as events. Dr. (b) (4) explained that the risk associated with the 'Glenn' procedure is significantly higher if performed prior to four months of age. This procedure is optimally performed after five to six months of age, usually at nine to twelve months. The protocol will not provide criteria for electing to perform the 'Glenn' procedure. This will be determined by the individual investigators. The total number of events will be counted and no time-to-event analysis is planned. Once the 'Glenn' procedure is performed, the patient will be discontinued from the study.

Discussion Point #9: Sample size and estimated event rate

The sizing of the study will depend on the estimated event rate and risk reduction. The Agency requested that the sponsor provide us with an objectively documented estimate of the event rate in this population. We did not believe the sponsor had adequately done this. It is important in issuing a Written Request that we are convinced that the study is adequately designed to provide a real chance of obtaining definitive information.

Based on the literature, the sponsor believes the estimated event rate for death between the first and second procedures is about 15%. Furthermore, based on published data, a 10% rate of shunt thrombosis is expected. Finally, the rate of early 'Glenn' procedures (prior to four months of age) is estimated to be between 15 and 20%. Since there will be some overlap between the three outcome endpoints, the sponsor adjusted the expected composite endpoint event rate to be approximately 35%.

The sponsor noted that their estimated treatment effect size is consistent with the CAPRIE findings, as well as clopidogrel data in the prevention of subacute stent thrombosis.

Discussion Point #10: Bleeding events

The investigator will determine the course of action to take for study subjects who experience bleeding events. This is not specified in the protocol. Provided the subject continues in the study, he/she will continue to be counted.

Discussion Point #11: Written Request

The Agency recommended that the sponsor look at the Written Requests available to them on the CDER website. Sanofi-Synthelabo should draft and submit a Written Request. In the Request, the sponsor should provide an adequate basis for the proposed sample size, but should not specify a particular number. The more specific the Written Requests/Agreements, the more difficult it is, usually, for the sponsor to obtain exclusivity. The Agency will most likely rewrite the Written Request and it is possible to amend a Written Request at any time prior to the submission of the study results.

Conclusion

In summary, the following agreements and conclusions were reached during the meeting:

1. In the Written Request, the Agency will likely request a population PK/PD assessment (ADP-induced platelet inhibition) of the older pediatric age groups.
2. The Agency does not have a preference as to whether dose is expressed in terms of body surface area or body weight.
3. Once the sponsor has conducted the initial dose-ranging study and selected a dose for the efficacy study, they will discuss the findings and dose selection with the Agency prior to proceeding with the efficacy study.
4. For the dose-ranging study, the Agency recommended that the sponsor select doses as we originally suggested (select several doses with a 10-fold difference between doses). After evaluation for futility of the first several patients at the low dose, the sponsor could revise the low dose upward if it appears that it lacks any effect on platelet inhibition.
5. Doses that produce levels of exposure higher than what has been previously studied in adults should not be included in the dose-ranging study.
6. The proposed patient population is acceptable.
7. The proposed endpoints, total mortality, early bi-directional Glenn procedure (prior to four months of age), and shunt thrombosis requiring intervention, are acceptable.
8. The sponsor should provide the Agency with an objectively documented estimate of the event rate in this patient population.
9. After reviewing the Written Requests available on the CDER website, the sponsor should draft and submit a Written Request. In the request, the sponsor should provide

an adequate basis for the proposed sample size, but should not specify a particular number. The Agency will likely rewrite the Written Request.

Signature, Meeting Recorder: Colleen LoCicero

Concurrence, Meeting Chair: Robert Temple, M.D.

cc: orig IND 34,663
HFD-110
HFD-110/Matthews
HFD-110/LoCicero
HFD-101/Temple

drafted: 8/10/00 finaled: 8/30/00

rd:
Temple 8/16/00
Behrman 8/30/00
Fredd 8/14/00
Rodin 8/14/00
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Lawrence 8/11/00
Robbie 8/14/00

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Transmitted to FAX Number:	(610) 889-6993
Attention:	Nancy Barone Kribbs
Company Name:	Sanofi-Synthelabo Inc.
Phone:	(610) 889-6425
Subject:	meeting minutes
Date:	4/21/00
Pages including this sheet:	7
From:	**Colleen LoCicero**
Phone:	**301-594-5334**
Fax:	**301-594-5494**

Nancy,

The minutes from our March 28, 2000 meeting regarding IND 34,663 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen
cc: orig IND 34,663
HFD-110
HFD-110/Matthews
HFD-110/LoCicero

Minutes of a meeting

Date of meeting:	March 28, 2000
Application:	IND 34,663
Product:	Plavix (clopidogrel) Tablets
Sponsor:	Sanofi-Synthelabo Inc.
Purpose:	to discuss pediatric program proposal
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Colleen LoCicero
Participants:	
FDA	
Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Rachel Behrman, M.D.	Deputy Director, HFD-101
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Steven Rodin, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Acting Team Leader, Statistical, Division of Biometrics I (HFD-710)
John Lawrence, Ph.D.	Statistician, HFD-710
Patrick Marroum, Ph.D	Team Leader, Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I (HFD-860)
Gabriel Robbie, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Florian Zielinski, Ph.D.	Chemist, Division of New Drug Chemistry I (HFD-810)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Sanofi-Synthelabo Inc.	
Jean Bouthier, M.D.	Vice President, Cardiovascular and Thrombosis Clinical Development
Christophe Gaudin, M.D.	Director, Cardiovascular and Thrombosis Clinical Development
Richard Gural, Ph.D.	Vice President, Regulatory Affairs
Ann Hards, Ph.D.	Director, Regulatory Affairs
Nancy Kribbs, Ph.D.	Assistant Director, Regulatory Affairs
Jose Necciari, Ph.D.	Director, Clinical Pharmacokinetics
Bristol-Myers Squibb	
Melvin Blumenthal, M.D.	Group Director, Clinical Cardiovascular Research and Development
Mary Ellen Norvitch, Ph.D.	Director, Cardiovascular Products, Regulatory Science

Consultants

(b) (4)

[redacted]

Background

The sponsor requested this meeting to discuss their proposal for a pediatric program for clopidogrel in patients with a Blalock-Taussig shunt due to congenital heart disease.

The meeting

Discussion Point #1: Essential components for pediatric program

The Agency believes the clopidogrel pediatric program should address the following concerns:

1. Doses for the entire range of pediatric age groups
2. Whether there is a true need for clopidogrel in this population
3. The studies need to evaluate a clinically meaningful endpoint

The Agency would not object to the proposed study, but we would not issue a written request for the study, as proposed, as we do not believe the study would address the above concerns.

Discussion Point #2: Pharmacodynamic assessment

The Agency suggested an initial pharmacodynamic assessment in a variety of pediatric age groups (five groups, including neonates) to assess platelet inhibition relative to dose to establish doses that would provide platelet inhibition in children similar to that achieved in adults after 10 days of clopidogrel administration. (There is a lag-time of 0-10 days to achieve peak pharmacodynamic effects for clopidogrel in adults.) The doses studied should differ by factors of 10, if possible, to characterize the dose-response curve. Dr. Lipicky suggested looking at 0.001, 0.01 and 0.1 mg/kg doses. Other doses that characterize the curve could also be acceptable. The endpoint would be the degree of ADP-provoked platelet inhibition.

The sponsor believed this proposal would be difficult, noting that such an assessment could not be done in normal volunteers. The Agency suggested that this assessment be carried out in patients with any vascular shunt. The Agency acknowledged that it might not be possible to assess the pharmacodynamics in all age groups.

Discussion Point #3: Clinical Endpoint

The initial pharmacodynamic assessment could then be followed by a clinical study that measures clinically meaningful endpoints, such as the need to revise a shunt, embolus, etc., in pediatric patients of all ages that have any kind of vascular shunt.

Luminal narrowing alone does not appear to be a known surrogate for events. If it is linked to clinical outcome, the sponsor should use these clinical outcomes as endpoints. Without clinically meaningful endpoints, e.g., the need to revise a shunt, etc., the study of luminal size is interesting, but would not provide sufficient information to warrant exclusivity.

The sponsor believed events would be too few to provide a sufficient number to adequately power such a study. The Agency noted the sponsor's concern that luminal narrowing often forces physicians to perform the "bi-directional Glenn" procedure earlier than planned and asked that the sponsor further explain this concern.

Dr. (b) (4) explained that modified Blalock-Taussig shunts are placed in patients with congenital heart defects to provide a supply of pulmonary blood flow. The shunts are usually placed between 0 and 14 days and kept in place for the first few months of life. At that time, in many cases, a "bi-directional Glenn" procedure is performed. It is not possible to perform the "bi-directional Glenn" procedure in neonates due to high pulmonary vascular resistance. At two to three months, it is possible to perform the "Glenn" procedure, although the risk to the patient is still high. It is optimal if the "bi-directional Glenn" procedure can be delayed until 4 to 6 months of age. If the shunt narrows too quickly and the physician is forced to perform the "bi-directional Glenn" prematurely, at, for example, six to eight weeks, the risk to the patient is greatly increased. The Agency suggested that the sponsor focus on this factor (acceleration of the surgery schedule) as an endpoint. The sponsor noted that other factors might also affect the decision to move up the "Glenn" procedure, introducing a lot of variance. The Agency did not believe this to be a major concern and believed it more important to have a clinically meaningful endpoint.

Dr. Fenichel noted the sponsor's concern that they might not have enough events if they assess only mortality/morbidity of those patients who undergo the "Glenn" procedure early. He noted that, alternatively, the sponsor might consider assessing developmental milestones at a pre-specified age for those children whose surgery schedules were accelerated to determine whether they differ developmentally from those children who received clopidogrel and were therefore able to maintain their original surgery schedule. The sponsor did not believe it would be possible to detect developmental differences until the children were school-age, which would require long-term follow-up. Long-term follow-up is a possibility since the sponsor's patent does not expire until 2011. The Agency is required to establish a schedule in the Written Request, but the schedule should be appropriate for the needed duration of study.

Discussion Point #4: Additional consideration

Dr. Fenichel noted the possibility that over the next few years, an antiplatelet therapy might come along that becomes the medical standard in this setting. It might even be clopidogrel. If this happens, it might make recruiting both investigatipnal sites and patients into this program difficult. It therefore might be wise to begin recruiting for this program as soon as a program has been established.

Discussion Point #5: Study population

The Agency acknowledged the sponsor's concerns about having a sufficient number of events to power the study, noting that this was the reason we suggested they not limit the study to modified Blalock-Taussig shunts, but include pediatric patients with all types of vascular shunts (i.e., dialysis shunts, etc.). This should allow for a considerable increase in sample size. The sponsor is concerned with how to appropriately power the study for such a patient population, as there would be considerable differences in endpoint frequency between shunt subgroups. They asked the Agency how we would interpret the results if the population included all vascular shunts and one subset looked promising, while another did not. Additionally, the sponsor asked what indication could be expected from such a study. The Agency believed if the overall result were positive, clopidogrel could be indicated in pediatrics for use in any vascular procedure in which vessel patency is a concern. It would not be necessary to demonstrate a statistically significant effect of clopidogrel in each individual vascular procedure subgroup.

The sponsor believed the effects in different shunt populations might differ and that some patient subpopulations might not receive all of clopidogrel's platelet inhibition effect. The Agency acknowledged this possibility, noting that if there were a subgroup within the vascular shunt population that was relatively small and in which the pharmacodynamic effect differed notably from the other subgroups, it would be acceptable to exclude this particular subgroup prospectively from the analysis.

Finally, the sponsor noted that expanding the population to include all vascular shunt patients would spread out the population, making the patients harder to identify. It would be administratively difficult to pool these patients.

Discussion Point #6: Sample size

If the sponsor opts to follow the Agency's recommendations and can identify a clinically meaningful endpoint, the sponsor should design and size the study to detect a 20% reduction in events compared to placebo to demonstrate efficacy. The study should be sized by events and not subjects.

Discussion Point # 7: Dose selection

It would be acceptable to use doses that result in higher exposure than that which has been studied in adults, provided the endpoints are clinically relevant.

Discussion Point #8: Pharmacokinetics

Noting that we had already suggested revisions to the program that would considerably increase the needed sample size, the Agency did not believe it necessary for the sponsor to assess pharmacokinetics, only pharmacodynamics, in the pediatric program.

Conclusion

The Agency outlined several options for capturing a sufficient number of events to adequately power the study:

1. Continue the study to 2009, so that all subjects are captured. This should provide about 500-600 events.
2. Expand the idea of what makes an event, i.e., premature surgery, hospitalization, etc.
3. Rather than events, assess various measures, such as mortality, developmental markers, years outside the hospital during the first year, etc., at a pre-specified age (perhaps age 7).

Dr. Temple believed that we would not be able to issue a written request for clopidogrel, at this time on the basis of this proposal, as it fails to evaluate a clinically meaningful outcome. Although we would not require a complete protocol prior to issuing a Written Request, the sponsor would need to propose a study with clinically valuable endpoints. The Agency would like to see a composite endpoint of clinically meaningful events.

Signature, Meeting Recorder: Colleen LoCicero Colleen Locicero

Concurrence, Meeting Chair: Robert Temple Robert Temple, M.D.

cc: orig IND 34,663
HFD-110
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drafted: 4/7/00 finaled: 4/20/00

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Temple 4/18/00
Behrman 4/14/00
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Rodin 4/13/00
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