

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202057Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

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

NDA NUMBER

202-057

NAME OF APPLICANT/NDA HOLDER

Amarin Pharmaceuticals Ireland Limited

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)

Vascepa

ACTIVE INGREDIENT(S)

icosapent ethyl

STRENGTH(S)

1 gram

DOSAGE FORM

Capsule

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

6479544

b. Issue Date of Patent

November 12 2002

c. Expiration Date of Patent

June 29 2021

d. Name of Patent Owner

Amarin Neuroscience Limited

Address (of Patent Owner)

c/o Byrne Wallace - Tom Maher; 2 Grand Canal Square

City/State

Dublin 2

ZIP Code

Ireland

FAX Number (if available)

Telephone Number

+353 (0)1 6699 020

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)

Amarin Pharma Inc.
c/o Peggy Berry

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

12 Roosevelt Ave.

City/State

Mystic, CT

ZIP Code

06355

FAX Number (if available)

(860) 572-4940

Telephone Number

(860) 572-4979

E-Mail Address (if available)

peggy.berry@amarincorp.com

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

Yes No

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

Yes No

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

2. Drug Substance (Active Ingredient)		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. Drug Product (Composition/Formulation)		
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4. Method of Use		
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
14	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VASCEPA is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) triglycerides. (b) (4)	
5. No Relevant Patents		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes

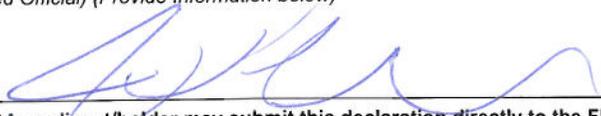
6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



19 Sept 2011

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

Amarin Pharmaceuticals Ireland Limited (John F. Thero, Director)

Address

c/o Amarin Pharma Inc.
12 Roosevelt Ave., 3rd Floor

City/State

Mystic, CT

ZIP Code

06355

Telephone Number

(860) 572-4979

FAX Number (if available)

(860) 572-4949

E-Mail Address (if available)

john.thero@amarincorp.com

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

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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

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 # 202057

SUPPL #

HFD #

Trade Name VASCEPA

Generic Name icosapent ethyl

Applicant Name Amarin Pharmaceuticals Ireland Limited

Approval Date, If Known 7/26/2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

5

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

Determination of whether this application qualifies for 3 or 5 years of exclusivity was not finalized by the goal date. The final decision will be made post-approval and this form will be completed at that time.

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

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: Kati Johnson

Title: Senior Regulatory Project Manager

Date: July 27, 2012

Name of Office/Division Director signing form: Eric Colman, MD

Title: Deputy Division Director, Division of Metabolism and Endocrinology Products

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.

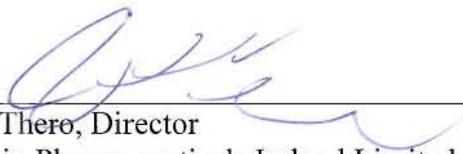
/s/

KATI JOHNSON
07/27/2012

ERIC C COLMAN
07/27/2012

1.3.3 Debarment certification

Amarin Pharmaceuticals Ireland Limited 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.



John Thero, Director
Amarin Pharmaceuticals Ireland Limited

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202057 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: VASCEPA Established/Proper Name: icosapent ethyl Dosage Form: capsules		Applicant: Amarin Pharmaceuticals Ireland Limited Agent for Applicant (if applicable): Amarin Pharma Inc.
RPM: Kati Johnson		Division: Metabolism and Endocrinology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>7/26/2012</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None	

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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>X</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP 7/26/2012</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>X</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p>N/A</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	12/19/2011-Initial OK 6/11/2012-Final OK
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 12/12/2011 <input checked="" type="checkbox"/> DMEPA 12/23/2011 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 6/12/2012 <input type="checkbox"/> ODPD (DDMAC) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PharmTox 7/25/2012
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing Review 7/26/2012
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) 6/5/2012
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 6/5/2012
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	X Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>3/21/2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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 <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 3/16/2011
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 7/14/2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/26/2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	7/26/2012
• Clinical review(s) <i>(indicate date for each review)</i>	7/26/2012, 11/15/2011
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See page 16 of 7/26/2012 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 6/5/2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 5/17/2012,
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 6/1/2012, 11/10/2011
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 6/5/2012, 11/18/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc no sep stat review
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 4/11/2012 Included in P/T review, page 65
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 7/26/2012, 5/30/2012, 3/19/2012, 11/10/2011
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 5/23/2012, 11/9/2011
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	page 74 of 3/19/2012 CMC review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 7/26/2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ 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.

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/s/

KATI JOHNSON
07/27/2012

From: [Johnson, Kati](#)
To: [Peggy Berry](#)
Subject: RE: NDA 202057. VASCEPA, revised labeling
Date: Thursday, July 26, 2012 5:54:10 AM

We note your agreement with the labeling sent to you 7/25/2012 at 12:26 pm.
Kati

From: Peggy Berry [mailto:peggy.berry@amarincorp.com]
Sent: Wednesday, July 25, 2012 12:58 PM
To: Johnson, Kati
Subject: RE: NDA 202057. VASCEPA, revised labeling

This looks great.

Do you need me to make this into an official submission or not – sorry I might have asked that before and I can't remember...

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, July 25, 2012 12:26 PM
To: Peggy Berry
Subject: NDA 202057. VASCEPA, revised labeling
Importance: High

Peggy,

Here is the revised PI/PPI. It is identical to what you sent me, with the following exceptions:

-In the PPI, we have deleted the statement (b) (4) under

"What should I tell my doctor before taking VASCEPA?"

-In the PPI, under **"What are the possible side effects of VASCEPA?"**, we have revised the sentence (b) (4) to read "This is not the only side effect of VASCEPA", since there is only a single side effect mentioned.

Please just e-mail me back and say that the labeling is acceptable, if that is the case. I will archive that e-mail and you will not have to submit anything additional.

Thanks, Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

Legal Notice Regarding Confidentiality and Authorized Access: This message is confidential and contains information which may be legally privileged, and protected from disclosure. It is intended for the stated addressee(s) only. Access to this email by unintended or unauthorized persons is prohibited. If the reader of this message is not the stated addressee, or an employee or agent responsible for delivering this message to the stated addressee(s), you are hereby notified that any disclosure or copying of the contents of this e-mail or any action taken (or not taken) in reliance on it is unauthorized and unlawful. If you are not the addressee, please inform the sender immediately and delete the message from your computer.

12 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

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/s/

KATI JOHNSON
07/26/2012

From: [Raggio, Miranda](#)
To: [Johnson, Kati](#); [Galliers, Enid M](#)
Cc: [Ripper, Leah W](#); [Bertha, Amy](#); [Duvall, Beth A](#); [Raggio, Miranda](#)
Date: Monday, June 04, 2012 2:49:39 PM

Hi Kati,

We discussed NDA 202057 at today's 505(b)(2) clearance meeting and you are cleared for action from a 505(b)(2) perspective.

Please make the following changes to your 505(b)(2) assessment before archiving in DARRTS for your approval action:

Revisions needed to (b)(2) assessments:

- *Question 2: Remove Epadel from the table because it is not a listed drug (b/c it is not approved in the U.S.).*
- *Question 3: Elaborate on the nonclinical bridging study, stating, for example, that Amarin conducted a 4-week rat comparative toxicity and toxicokinetics study with Vascepa (AMR101) and Epadel. Additionally, state the reason why the bridging study was needed, for example, note that Epadel was cited in the literature and Amarin is relying on that published literature.*
- *Question 14: Check the first box, "No patent certifications are required..."*

Thanks for a great job on your 505b2 assessment and for your timely responses to our inquiries.

miranda

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Regulatory Affairs Team
Immediate Office/Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3310
Silver Spring, MD 20993
301-796-2109
Miranda.Raggio@fda.hhs.gov

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/s/

KATI JOHNSON
06/05/2012

Executive CAC

Date of Meeting: April 10, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Hanan Ghantous, Ph.D., DAVP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Pharm Tox Supervisor
Stephanie Leuenroth-Quinn, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Stephanie Leuenroth-Quinn

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

NDA #202057

Drug Name: Vascepa (icosapent ethyl, ethyl-EPA, AMR101)

Sponsor: Amarin Pharma

Background:

Vascepa (ethyl-EPA) is the ethyl ester of eicosapentaenoic acid, a long chain polyunsaturated omega-3 fatty acid (C20:5). The sponsor is developing Vascepa for the treatment of hypertriglyceridemia. Ethyl-EPA is rapidly converted to EPA by pancreatic lipase, is taken up by enterocytes and repackaged into chylomicrons before secretion into the lymph and eventual systemic absorption. Omega-3 fatty acids will compete with other saturated or unsaturated fatty acids for membrane incorporation throughout the body and can influence cellular signaling, reduce inflammation and decrease triglyceride production by the liver.

Tg.rasH2 Mouse Study:

The sponsor conducted a 6-month TgRasH2 mouse study in which ethyl-EPA was administered at doses of 0 (water control), 500, 1000, 2000 and 4600 mg/kg/day ethyl EPA by oral gavage. The ethyl EPA was administered neat, at increasing volumes. The incidence of skin/subcutis squamous cell papillomas of the proximal tail increased with dose in male mice only (0/25-0/25-0/25-1/25-5/25), and was statistically significant (pairwise analysis: P = 0.0248). The sponsor attributed these tumors to local irritation, inflammation and subsequent cellular proliferation from fecal excretion of excess oil. There was an increased incidence of mesenteric lymph node thrombosis of the perimesenteric vein as well as ileum mesenteric vein thrombosis and inflammation.

Similar to males, female mice had histopathology findings of acanthosis/ hyperkeratosis at the proximal tail along with ulcer/ erosion and inflammation. Clinical signs and macroscopic observations also showed females with nodules at the proximal tail, yet these were not papillomas by histopathology. Systemic exposure of EPA in females was slightly higher than in males.

Rat Carcinogenicity Study:

A two-year rat carcinogenicity study was conducted without prior Exec-CAC concurrence. Wistar rats were administered approximately 91, 273 and 911 mg/kg/day ethyl-EPA by oral gavage. The ethyl EPA was administered neat, at increasing volumes. Two controls were used where control 1 was corn oil (1.0 mL/kg) and control 2 was undosed. The HD female group was terminated at week 98 due to an increase in decedents in this group and deteriorating condition. The incidence of combined hemangiomas/ hemangiosarcomas at the mesenteric lymph node in females was considered drug related when compared to the undosed control (0/50-0/50-5/50-6/50) and was statistically significant (pairwise analysis: $P = 0.0047$). As EPA first passes from the small intestine through the lymph before systemic absorption, the concentration of this fatty acid would be highest at the mesenteric lymph node; therefore this site is considered independently. Additional evidence that the mesenteric lymph node may be physiologically relevant is the increased incidence of thrombosis (perimesenteric vein of mesenteric lymph node) in both sexes of the 6-month Tg.rasH2 mouse study. When hemangiomas/ hemangiosarcomas from all sites were combined, no drug related increase in this tumor in either sex was observed.

No other neoplasms were statistically significant by the criteria used by the Exec-CAC.

Executive CAC Recommendations and Conclusions:

Tg.rasH2 Mouse:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms in females and that the skin/subcutis papillomas in the tail of males were drug-related but not relevant to humans.

Rat:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no neoplasms clearly drug-related in male rats. Mesenteric lymph node hemangiomas/ hemangiosarcomas appeared to be drug related in female rats. However the incidences of hemangiomas/ hemangiosarcomas at all sites, combined, were not statistically significantly increased. The Committee noted that the increased incidence of mesenteric lymph node thrombosis of the perimesenteric vein as well as ileum mesenteric vein thrombosis and inflammation, both seen in the TgRasH2 mice and the high drug exposure at the mesenteric lymph nodes in the rats suggest that the mesenteric lymph node hemangiomas/ hemangiosarcomas in rats are drug-related.

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

cc:\

/Division File, DMEP

/K. Davis-Bruno, Team leader, DMEP

/S. Leuenroth-Quinn, Reviewer, DMEP

/K. Johnson, PM, DMEP

/A. Seifried, OND IO

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

/s/

ADELE S SEIFRIED
04/11/2012

DAVID JACOBSON KRAM
04/11/2012

Johnson, Kati

From: Greeley, George
Sent: Tuesday, March 27, 2012 2:04 PM
Johnson, Kati
Subject: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Parks, Mary H
NDA 202-057 Vascepa
Importance: High
Attachments: 1_Pediatric_Record.pdf

Hi Kati,

This email serves as confirmation of the review for Vascepa (Icosapent Ethyl) conducted by the PeRC PREA Subcommittee on March 21, 2012.

The Division presented a full waiver of studies in pediatric patients because there were too few children with disease/condition to study for the indication of hypertriglyceridemia.

The PeRC agreed with the Division to grant a full waiver for this indication.

The pediatric record is attached for Vascepa.



1_Pediatric_Re
ord.pdf (56 KB).

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

 Please consider the environment before printing this e-mail.



NDA 202057

DISCIPLINE REVIEW LETTER

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
1430 Route 206, Suite 200
Bedminster, NJ 07921

Dear Ms. Berry:

Please refer to your September 25, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vascepa (icosapent ethyl) Capsules, 1 gram.

We also refer to your amendments dated January 30 and February 6, 2012.

Our review of the chemistry, manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

1. DMF 15062 is inadequate. Comments have been communicated to the DMF holder.
2. Since the maximum daily dose is > 2 g, the ICH Q3A(R2) identification and qualification threshold for related substances for impurities in drug substances is 0.05%. Therefore, submit revised drug substance specifications to tighten the proposed limit for 'related substances, others' (b)(4). In addition, provide data identifying and qualifying all impurities present above (b)(4). Because of the harsh manufacturing process and the resulting impurity profile of your drug substance, a tighter threshold for qualification of impurities is required.
3. The application includes only 3-months stability data (long-term and accelerated) for one product batch manufactured by Catalent. An expiration dating period cannot be determined based on such limited data. As previously conveyed to you in our December 8, 2011 letter, we again strongly recommend that Catalent be submitted in a postapproval supplement with all the necessary supporting data (i.e., withdrawn from the current NDA submission).

Please respond to the following request at your earliest convenience.

4. Submit revised comparability protocols that have been modified as follows:
 - a. For the drug substance process optimization, revise the stability commitment to state that data will be submitted from three batches placed on long-term stability.
 - b. For the additional packaging configurations of the drug product, revise the protocol to state that the required labeling changes will be submitted in a Supplement - Changes Being Effected in 0 Days.
 - c. For a new manufacturing site of the drug product, revise the protocol to state that data will be submitted from three batches placed on long-term stability.

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

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ENID M GALLIERS
03/26/2012



NDA 202057

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
1430 Route 206, Suite 200
Bedminster, NJ 07921

Dear Ms. Berry:

We acknowledge receipt on December 30, 2011, of your December 30, 2011 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

to

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
1430 Route 206, Suite 200
Bedminster, NJ 07921

for the following new drug application:

NDA 202057 for VASCEPA (icosapent ethyl) Capsules, 1 gram.

We have revised our records to reflect this change.

Please cite the NDA 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 Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
01/03/2012



NDA 202057

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AmarinPharma Inc.
Mystic Packer Building
12 Roosevelt Ave, 3rd floor
Mystic, Connecticut 06355

Attention: Peggy Berry, MBA
Vice President, Quality & Regulatory Affairs

Dear Ms. Berry:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received on September 26, 2011, submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Icosapent Ethyl Capsules, 1000 mg.

We also make refer to your September 23, 2011, correspondence, received September 26, 2011, requesting review of your proposed proprietary name Vascepa.

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

The proposed proprietary name, Vascepa, will be re-reviewed 90 days prior to approval. If **any** of the proposed product characteristics as stated in your September 23, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kati Johnson at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/19/2011



NDA 202057

FILING COMMUNICATION

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

Dear Ms. Berry:

Please refer to your New Drug Application (NDA) dated September 25, 2011, received September 26, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for VASCEPA (icosapent ethyl) Capsules, 1 gram.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **July 26, 2012**.

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, midcycle, 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 **June 20, 2012**.

During our filing review of your application, we identified the following potential review issues:

Your 505(b)(2) application did not contain a complete nonclinical package. Specifically, you are relying on non-clinical literature references published by Mochida with Epadel (an approved ethyl-EPA approved in Japan). However, you did not provide an appropriate comparative bridge to Epadel to allow reliance on this data. In lieu of a direct side-by-side comparison of Vascepa (AMR101) to Epadel, published PK studies of Epadel were compared to PK data obtained from AMR101 nonclinical studies. Evaluation of these data does not directly compare the two

products as methodologies, radiolabeling, and length of administration are not similar between the products. Additionally, there was no supportive evidence of product comparability (*i.e.* impurity levels) due to the lack of any extensive chemical characterization between Epadel and Vascepa, submitted to NDA 202057.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical

1. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

Pharmacology/Toxicology

2. As there is no adequate bridging information to Epadel, conduct an appropriate nonclinical study (*e.g.* 28-Day repeat dose toxicology study in the rat) to demonstrate at a minimum, PK comparability between Epadel and Vascepa (AMR101), so that you may rely on published Epadel literature for your 505(b)(2) application.

Chemistry, Manufacturing, and Controls

3. In the NDA, you include the drug substance specifications from the drug substance manufacturer and from the drug product manufacturer Banner. Reference is made to DMF 25289 for the drug substance specification from the drug product manufacturer Catalent. Provide a copy of the Catalent drug substance specification in the NDA. In addition, clarify which drug substance specification will serve as the regulatory specification (*i.e.*, for FDA's method validation and GMP enforcement purposes).
4. A comparability protocol cannot be located in the NDA even though you proposed one at the Pre-NDA meeting. As stated in FDA's 2003 draft guidance "Comparability Protocols – CMC Information", the protocol should be submitted either in the original NDA or in a post-approval supplement (prior-approval) for FDA's approval prior to the applicant's initiation of the protocol studies. Clarify whether you still intend to use a comparability protocol for qualifying a new drug substance manufacturer.
5. Justify the lack of Microbial Limits in the drug substance specifications. The drug substance is naturally derived and such an attribute should be included in the specification.
6. Include in the drug substance specifications tests and acceptance criteria for contaminants commonly found in fish oil (b) (4)

(b) (4). Provide safety information to support the proposed acceptance criteria.

7. Submit the Catalent product composition to the NDA.
8. The NDA includes only 1-month stability data (long-term and accelerated) for one product batch manufactured by Catalent. An expiration dating period cannot be determined based on such limited data. We strongly recommend that Catalent be submitted in a post-approval supplement (i.e., withdrawn from the current NDA submission) with all the necessary supporting data (comparative in-vitro testing, at minimum 3-month long-term and accelerated stability data for three product batches at no less than 10% commercial scale).

Product Quality Microbiology

9. Submit the test methods and data sets verifying the suitability of the use of the stated microbial limits test with the drug product.

Biopharmaceutics

10. Provide the method development report of the disintegration test including the parameters for the proposed disintegration test: Medium, Volume, Apparatus, Time, Procedure and Tolerances.
11. Submit disintegration results generated on batches used in both clinical and stability studies. The specification will be set after FDA reviews the disintegration results generated from these batches.
12. Submit comparative disintegration test results comparing batches manufactured at Banner and Catalent and specify the manufacturing site to be used to manufacture the commercial product.
13. Submit comparative disintegration test results comparing the pilot scale batches and the intended commercial scale batches
14. Submit information or data to support that the fill material does not change with time.

Office of Scientific Investigations

15. Please identify for Study 01-01-0016:
 - a. Location of Trial Master File and Clinical Investigator Master Files [actual physical site(s) where documents are maintained and would be available for inspection].
 - b. Current name, address, and contact information of all CROs used in the conduct of the clinical trial.
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies.

- d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.) if not included with “a” above.

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

1. Under Table of Contents (TOC), if a section of subsection is omitted from the FPI and TOC, the heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
2. Under Table of Contents, all section headings must be in bold type, and subsection headings must be indented and not bolded.
3. There should be no periods after numbers for sections and subsections in the Full Prescribing Information and the Table of Contents.
4. Regarding Contraindications, the labeling should not include theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
5. In the Highlights section, the following verbatim statement must be included: “See 17 for Patient Counseling Information and FDA-approved patient labeling” (since you are proposing patient information labeling).

We request that you resubmit labeling that addresses these issues by January 1, 2012. The resubmitted labeling will be used for further labeling discussions.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Your application requests a partial waiver of pediatric studies for ages 0 to 10 years, and a deferral request for ages 11 to 18 years. Your application does not address pediatric patients who are 10 years of age. Within 30 days of the date of this letter, please amend your application to fully address PREA across the entire pediatric age range, 0 to 17 years.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN

12/08/2011

Eric Colman for Mary Parks

Record of 10-05-11 Telecon and 10-06-11 Email communication re NDA 202057

Between Enid Galliers, CPMS, DMEP, CDER, FDA
And
Peggy Berry, Regulatory Contact, Amarin Corporation

BACKGROUND: NDA 202057 icosapent ethyl capsules was submitted as a 505(b)(1) application on Sept. 25, 2011, received Sept. 26, 2011. The filing date is Friday, November 25, 2011, and the filing meeting is scheduled for Monday, November 14, 2011.

Apparently, the applicant will rely in part on published preclinical data for another product that is approved in Japan and for which it does not currently have right of reference. Amarin has been concerned about the possibility of receiving a Refusal to File (RTF) action and whether they can amend the application to avoid RTF. Additional questions were raised but the attached email summarizes the essential points of the communications between Ms. Berry and me.

Galliers, Enid M

From: Galliers, Enid M
Sent: Thursday, October 06, 2011 4:26 PM
To: 'Peggy Berry'
Subject: RE: NDA 202057 - additional follow up

Peggy,

I've modified your text a little and added a note reflecting guidance I received today that confirmed that you can switch back to a (b)(1) after filing.

Regards,

Enid

From: Peggy Berry [mailto:peggy.berry@amarincorp.com]
Sent: Thursday, October 06, 2011 1:05 PM
To: Galliers, Enid M
Subject: RE: NDA 202057 - additional follow up

Hi Enid,

Thanks again for your time yesterday. I think that you provided the final clarity that we needed so that we can make a decision going forward. I prepared a brief summary of our call yesterday and I wanted to run it by you quickly to make sure that I got everything right.

The FDA (Enid Galliers) confirmed that if we are relying on literature that we believe is necessary for approval we should switch our submission to be a (b)(2).

The FDA confirmed that being a (b)(1) vs. a (b)(2) does not impact our ability to get exclusivity as an NCE of 5 years because that decision is made completely separately from the type of filing.

The FDA confirmed that it is not the division's policy or practice to contact the sponsor in advance of issuing an RTF to allow them to make the corrections or changes needed to make it fileable. This is generally because there is **either** not enough time for **the applicant to submit an amendment, much less for FDA** to review **any** amendment that **might be** submitted to ensure that it is appropriate to file the application with the change. Because of the timing of our filing date (right before Thanksgiving), she said the problem is further magnified because people may not be in the office **or otherwise available** to do the review.

Finally, the FDA further **confirmed** that if we switch now to a (b)(2) and we later get right of reference to the Mochida data, we can switch back to a (b)(1) if we want to. She said that if this switch is made by month 7, they would NOT extend the timeline for their first response. She also said that if it's done after month 7, and it is not requiring them to review new data that is not already part of the publication, they may not extend the review clock at that time either, but it depends on what's submitted and on discussions with their policy attorneys. **(Additional notes: The only caveat to add is if the literature cites a branded product, then you also need to cite reliance on that listed drug and provide the appropriate patent cert or statement to address reliance on the listed drug cited in literature. And whether you do this before or after filing also has no consequence. A form FDA 356h**

should be included in each submission and the 505(b)(1) or 505(b)(2) should be adjusted as needed.

Thanks!
Peggy

From: Peggy Berry
Sent: Tuesday, October 04, 2011 5:55 PM
To: Galliers, Enid M
Subject: RE: NDA 202057 - additional follow up

11 is great. I will call you then.

From: Galliers, Enid M [<mailto:Enid.Galliers@fda.hhs.gov>]
Sent: Tuesday, October 04, 2011 5:47 PM
To: Peggy Berry
Subject: RE: NDA 202057 - additional follow up

Hi Peggy,

Would 11:00 AM be convenient for you? Will you call me at my office number (below)?

Thanks,

Enid

From: Peggy Berry [<mailto:peggy.berry@amarincorp.com>]
Sent: Tuesday, October 04, 2011 5:44 PM
To: Galliers, Enid M
Subject: RE: NDA 202057 - additional follow up

Hi Enid,
Could we schedule a brief call for tomorrow? The morning works best for me, but any time that works for your schedule will be fine.

Thanks,
Peggy

From: Galliers, Enid M [<mailto:Enid.Galliers@fda.hhs.gov>]
Sent: Friday, September 30, 2011 3:17 PM
To: Peggy Berry
Subject: FW: NDA 202057 - additional follow up
Importance: High

Hello Peggy,

First, please contact me regarding this NDA during Kati's absence. Second, an application can be amended during the initial 60-day filing review period. However, the review team must have enough time to consider any amendments relevant to a filing decision prior to the filing meeting. Therefore, I recommend that your company carefully consider FDA's 1999 draft guidance for industry *Applications Covered by Section 505(b)(2)*, and if you decide to amend your NDA as a 505(b)(2), to assure delivery of the amendment by the end of October

so that the review team can evaluate fileability accordingly.

I will be available (preferably at a prescheduled time) to discuss the guidance with you next week. Please arrange a teleconference with me by email.

Regards,

Enid

Enid Galliers

Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

Submissions:

FDA, CDER, CDR
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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From: Johnson, Kati
Sent: Friday, September 30, 2011 12:11 PM
To: Galliers, Enid M
Subject: FW: NDA 202057 - additional follow up
Importance: High

From: Peggy Berry [<mailto:peggy.berry@amarincorp.com>]
Sent: Friday, September 30, 2011 11:26 AM
To: Johnson, Kati
Subject: NDA 202057 - additional follow up
Importance: High

Hi Kati,

I'm sure that you don't want to hear from me today – but, I have been asked to do an additional follow up with you before you go on vacation. We had a call with our Board last night and everyone still believes that we are a 505(b)(1). However, they are a little freaked out about not having the possibility to amend the application to be

a 505(b)(2) in the event that the FDA disagrees with us at day 45. All of the regulatory lawyers and other regulatory advisors who we have consulted with say that the FDA, as a general standard practice, allows the company to amend the NDA prior to issuing a RTF if the change can be made quickly – like 24 hours. As a small company, we can't survive having a RTF because it could put us out of business. So that's what they are having more struggle now than before is that it sounds like we won't have that opportunity here. Can you confirm for me that this is the case? Or, is there someone else that I could or should discuss this with while you're out? Thanks again for all of your help with this – I really do appreciate it!

Peggy

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/s/

ENID M GALLIERS
10/06/2011

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Wednesday, September 28, 2011 8:45 AM
To: 'peggy.berry@amarincorp.com'
Cc: Johnson, Kati

Dear Ms. Berry,

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 202-057 received September 26, 2011. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

- Please provide a contact name, phone number, fax number for the Drug Substance Manufacturer (Nisshin Pharma Inc, Japan)
- Please provide a statement that all the facilities are ready for GMP inspection.
- Please list all the drug substance manufacturers and drug product manufacturers together as an attachment to the Form 356H.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you

*Khushboo Sharma
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270*

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/s/

KHUSHBOO SHARMA
09/28/2011



NDA 202057

NDA ACKNOWLEDGMENT

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

Dear Ms. Berry:

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

Name of Drug Product: VASCEPATM (icosapent ethyl) Capsules, 1 g

Date of Application: September 25, 2011

Date of Receipt: September 26, 2011

Our Reference Number: NDA 202057

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 22057** submitted on September 25, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

mail or courier, to the following address:

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

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

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

KATI JOHNSON
09/27/2011



IND 102457

MEETING MINUTES

Amarin Pharma Inc.
Attention: Peggy Berry
VP, Head of Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

Dear Ms. Berry:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMR101 (ethyl-EPA) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2011. The purpose of the meeting was to discuss issues pertaining to your to-be-submitted NDA.

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

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes
DSI Documents

IND 102457
Meeting Minutes
Pre-NDA Meeting

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 16, 2011, 12:30 pm
Meeting Location: FDA White Oak Campus
Building 22, Conference Room 1315

Application Number: IND 102457
Product Name: AMR101 (ethyl-EPA) Capsules, 1 gram
Indication: Adjunct to diet to reduce triglyceride (TG) levels in patients with very high (≥ 500 mg/dL) TG levels.

Sponsor/Applicant Name: Amarin Pharma Inc.
Meeting Chair: Eric Colman, MD
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Division of Metabolism & Endocrinology Products

Eric Colman, MD-Deputy Director, Lipid Team Leader
Iffat Chowdhury, MD-Clinical Reviewer
Stephanie Leuenroth-Quinn, Pharmacology/Toxicology Reviewer
Bola Adeolu-Project Manager
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology

Sally Choe, PhD-Team Leader
Manoj Khurana, PhD-Reviewer

Office of Translational Sciences, Office of Biostatistics

Todd Sahlroot, PhD-Deputy Director, Division of Biometrics II
Japobatra Choudhury, PhD-Statistician

SPONSOR ATTENDEES

Amarin Pharma Inc.

Peggy Berry-VP, Regulatory Affairs and Quality
Rene Braeckman, PhD-Development Operations
Paresh Soni, MD, PhD-Senior VP, Development
William Stirtan, PhD-Sr. Director, Project Management & Nonclinical

BACKGROUND

AMR101 is ethyl EPA and is being investigated for the following indications:

1. As an adjunct to diet to reduce triglyceride (TG) levels in adults with very high (>500 mg/dL) TG levels

(b) (4)

To support the elevated TG indication above, the firm submitted Protocol **AMR-01-0016**, *A Phase 3 Multi-Center Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients with Fasting Triglyceride Levels ≥ 500 mg/dL and ≤ 1500 mg/dL*: The AMR101 **MARINE** Study. The design and planned analysis was found acceptable in a May 1, 2009 Special Protocol Agreement.

The IND was submitted May 22, 2009.

(b) (4) the firm submitted Protocol **AMR-01-01-0017**, *A Phase 3 Multi-Center Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients with Persistent High Triglyceride Levels (≥ 200 mg/dL and ≤ 500 mg/dL) Despite Statin Therapy*: The AMR101 **ANCHOR** Study. The design and planned analysis were found acceptable in a July 6, 2009 Special Protocol Agreement. The protocol was later revised, with regard to inclusion/exclusion criteria, on May 12, 2010.

(b) (4)

On August 12, 2010, the sponsor requested a Pre-NDA meeting to discuss chemistry, manufacturing and controls issues. In lieu of a meeting, written responses were provided on January 20, 2011.

The sponsor requested a Pre-NDA meeting on December 14, 2010. The meeting was granted on January 3, 2011.

2. DISCUSSION

Preliminary responses were provided to the sponsor on Tuesday, March 15, 2011.

The sponsor's questions are followed by our **bolded** preliminary responses, which are followed by any meeting discussion in underlined text. Any post-meeting comments are in *italicized* text.

NONCLINICAL (NC)

NC-1 Amarin considers that the new toxicity studies conducted with AMR101 along with the published studies conducted with ethyl-EPA (Epadel[®]) provide a comprehensive ICH M3 compliant package of preclinical information that can be used to assess the safety and

toxicity of AMR101. The available preclinical studies are summarized in Table 1, Table 2, Table 3, Table 4, and Table 5 and will be provided in the NDA. Amarin will rely on these data for the planned NDA and considers this a stand-alone preclinical package.

Does the FDA agree that the nonclinical information available for ethyl-EPA is sufficient to support a NDA filing?

FDA Preliminary Response:

Ultimately, the acceptability of the toxicology studies to support NDA filing can not be determined until the NDA has been submitted and all study reports have been reviewed. Preliminary review of the combination of submitted literature references and Amarin's nonclinical studies conducted with AMR101, appears sufficient; however the scientific adequacy remains a review issue. Since you plan to rely on nonclinical data which you do not own or have right of reference to, this application will not be considered a stand-alone package.

Genotoxicity experiments have shown that AMR101 is negative in the AMES assay, positive for clastogenicity (\pm S9), and negative in the mouse micronucleus assay. As final Agency review has not been completed for the 2-year rat or the 6-month transgenic RasH2 mouse carcinogenicity studies, it would be premature to comment on the adequacy and therefore safety assessment of these studies as a whole.

Meeting Discussion: None

NC-2 Amarin will provide electronic datasets for the carcinogenicity studies as SAS transport (Xport) files - version 5 (104-week rat study) and version 6 (26-week mouse study). Does the FDA agree to the proposed electronic data submission for the 2 carcinogenicity studies as described above?

FDA Preliminary Response:

FDA agrees to the proposal to submit the tumor data in SAS transport files. However, it is important to make sure that the data in the SAS transport files are in the FDA data format described in the guidance document entitled "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications".

Meeting Discussion: None

CLINICAL (CL)

CL-1 Does the FDA agree that at present, a deferral of the pediatric study requirement is acceptable?

FDA Preliminary Response: According to the Pediatric Research and Equity Act (PREA), at the time of the NDA submission, you must either submit a deferral, waiver, or the results of a pediatric study for the proposed indication(s). Since, to our knowledge, Amarin does

not have such a study, submission of a deferral or waiver will be necessary. You must state the specific age groups for which you are seeking a waiver/deferral and provide a justification for the request. The acceptability of the deferral/waiver will be determined during the course of the NDA review.

Meeting Discussion: The agency confirmed that the inclusion of a waiver/deferral request would render the submission a complete application for filing purposes, at least from a PREA perspective. The sponsor was reminded to address the entire pediatric group from 0 to 17 years of age.

CL-2 Does the FDA agree that Amarin, pending approval of AMR101 in adults, may submit to FDA a pediatric written request and be eligible for 6 months additional exclusivity upon completion of an agreed pediatric program?

FDA Preliminary Response: A Proposed Pediatric Study Request (PPSR) may be submitted at any time; whether the written request is issued is a review issue.

Meeting Discussion: None

CL-3 Amarin plans to submit a single study to support the efficacy of AMR101 for patients with very high (≥ 500 mg/dl) triglycerides. As there are no additional trials to integrate for efficacy, Amarin does not propose to submit an integrated summary of efficacy for AMR101, and will simply refer to the completed study report for MARINE (AMR-01-01-0016). Does the FDA agree with this approach?

FDA Preliminary Response: Under CFR 314.50(d)(5)(v), the Integrated Summary of Effectiveness (ISE) must include:

- **An integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication**
- **Evidence that supports the dosage and administration section of the labeling, including support for the recommended dosage and dose interval**
- **Effectiveness data analyzed by sex, age, and racial subgroups**
- **Evidence that is pertinent to individualization of dosing and the need for modifications of dosing for specific subgroups**

Further guidelines of what should be included in the ISE can be found in the *Guidance for Industry: Integrated Summary of Effectiveness*. If you plan to submit the study report for MARINE in lieu of the ISE, please make sure that the study report contains all the necessary elements of an ISE.

Meeting Discussion: The sponsor asked about inclusion of efficacy information from the ANCHOR study, which would add approximately 700 patients to the approximately 250 patients in the MARINE study. According to the firm, the MARINE study demonstrates that AMR101 therapy does not result in an increase in LDL. The study will be completed when the NDA is

submitted, but the final report will not be available at that time. The sponsor was notified that we would discuss this internally and provide a response in the finalized meeting minutes.

Post-Meeting Discussion- The study populations, inclusion and exclusion criteria as well as the different indications of the ANCHOR and the MARINE trials preclude the integration of the efficacy data from the trials. Thus your offer to include efficacy data from the ANCHOR study is not accepted as part of the Integrated Summary of Efficacy for the indication “as an adjunct to diet to reduce triglyceride levels in adult patients with very high ≥ 500 mg/dL triglyceride levels”.

CL-3.1 If yes, because this is an eCTD, is it acceptable to provide a link to the clinical study report from section 5.2.5.2? Or should no link be provided?

FDA Preliminary Response: A link to the clinical study report from section 5.2.5.2 is acceptable.

Meeting Discussion: None

CL-3.2 If No, please indicate what additional analyses are required?

CL-4 Amarin proposes that the Clinical Summary of Efficacy within Module 2 will also provide a full summary of the data obtained from the single pivotal efficacy study for patients with very high triglycerides (MARINE; AMR-01-01-0016). The Clinical Overview will take into account published literature as well as the pivotal efficacy study through the discussion. Does the FDA agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-5 Four (4) integrated databases will be presented to support the safety of AMR101 use in patients:

- Safety data from 2 multicenter, randomized, double-blind, placebo-controlled, Phase 3 clinical studies in subjects with hypertriglyceridemia
- Safety data from 8 multicenter, randomized, double-blind, placebo-controlled, Phase 2 and Phase 3 clinical studies in subjects with CNS disorders
- Safety data from 3 studies with healthy subjects treated with AMR101
- Safety data from all subjects treated with AMR101, regardless of study phase or indication

Does the Division agree that Amarin’s plan for integrating the safety data is acceptable?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-6 Amarin proposes to provide narratives for patient cases for deaths, discontinuations due to adverse events and serious adverse events for all AMR101 studies. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-7 Amarin proposes to provide case report forms (CRFs) for all deaths, discontinuations due to adverse events (AEs), and serious adverse events (SAEs) across all treatment arms within the hypertriglyceridemia studies with the NDA. CRFs for these types of events in other studies will be provided at Agency request. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-8 Within the subject NDA, Amarin plans to include the following information for each of the studies:

Full Study Report Module 5.3.1	Electronic Dataset Module 5.2.2	Summary of Results Module 2.7	Synopsis of Study Module 2.7.6
MARINE (AMR-01-01-0016)	MARINE (AMR-01-01-0016)	MARINE (AMR-01-01-0016)	MARINE (AMR-01-01-0016)
PK study (LA01.01.0009)		PK study (LA01.01.0009)	PK study (LA01.01.0009)
PK study (AMR-01-01-0018)		PK study (AMR-01-01-0018)	PK study (AMR-01-01-0018)
DDI study (AMR-01-01-0020)		DDI study (AMR-01-01-0020)	DDI study (AMR-01-01-0020)
		ANCHOR (AMR-01-01-0017)	ANCHOR (AMR-01-01-0017)
	ISS (includes all studies)		All CNS studies

Does the FDA agree with these contents?

FDA Preliminary Response (Clinical): Yes.

FDA Preliminary Response (Clinical Pharmacology): To enable a comprehensive and timely review, please submit raw concentration and PK parameter data for all applicable analytes (preferably as SAS transport files) for all PK/clinical pharmacology studies (LA01.01.0009, AMR-01-01-0018, and AMR-01-01-0020).

- The concentration data-set(s) should at least have the following columns: ID, Analyte Name, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.
- The PK parameter data set(s) should at minimum have the following columns: ID, Trial Number, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence.

In addition, include the electronic data-sets used for exposure-response analysis mentioned on page 34 section 3.2.7.4.4 in your submission. Also, include bioanalytical study reports supporting the concentration data in your submission.

Meeting Discussion: According to the background package, the sponsor has conducted in vitro studies to evaluate metabolic induction and inhibition potential of AMR101 on other drugs. The following CYP450 enzymes indicated a possible drug-drug interaction (in decreasing order of inhibition potential): 2C19, 2C9, 2C8 and 2B6. Based on their interpretation of the FDA Guidance: Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling (2006), Amarin conducted an in vivo study to test the inhibition of 2C19 and 2C8 (using respective substrates of omeprazole and rosiglitazone).

The agency interprets the guidance document differently. Positive in vitro studies tell you that there is sufficient signal to warrant conducting in vivo study(ies) and the agency would expect in vivo assessment of both 2C9 and 2B6 in the future NDA. In response to a question from the firm, the agency said they would file the NDA with draft report(s) reports of these in vivo studies, and the final reports would follow in 4 to 6 weeks.

During the internal meeting in preparation for this meeting with the sponsor, it was not clear what the proposed dosing regimen will be. The firm will be seeking approval for (b) (4) 4 g daily doses, and said they have information that exposure of 4 g daily dosing is equivalent to that of 2 g twice daily dosing used in the MARINE pivotal study. The agency told the sponsor that a simple pharmacokinetic comparison will not be sufficient to extrapolate twice daily dosing to once daily dosing. A justification is needed to show that the higher C_{max} with once daily dosing would not be a safety issue. In addition, information must be provided to demonstrate that efficacy would not be adversely affected with once daily regimen. Agency asked for additional clarification for the intention behind the development of 500 mg capsule used in the PK study; sponsor mentioned that 500 mg capsule is being used in studies conducted under CNS indication and for this submission, they are not proposing 500 mg capsule as part of NDA.

Post-Meeting Discussion:

The firm provided some text from the Drug Interaction guidance to support their position that negative interaction results in vivo for CYP enzymes with the largest [I]/K_i obviates the need to conduct in vivo evaluations of the other CYPs with smaller [I]/K_i. Based on this information,

we have the following comments:

We agree with the sponsor's comments on the draft DDI guidance language. However, the CYP inhibition potential that was identified with CYP2C9 can not be waived based on the guidance language because of the potential use of warfarin, the recommended sensitive CYP2C9 substrate and narrow therapeutic index drug. Therefore, depending on the in vivo DDI study with a sensitive CYP2C19 substrate, waiving the evaluation of in vivo DDI study with CYP2B6 is acceptable. We, however, continue to recommend that the sponsor conduct in vivo DDI studies evaluating the inhibition potential of CYP2C9 and 2C8 in addition to 2C19. These recommendations are based on the sponsor's claimed in vitro study results. If our review of the in vitro results do not agree with the sponsor's conclusions, these comments will not be applicable.

CL-9 Amarin studies were not designed to study withdrawal/rebound effects or abuse potential. Amarin believes that the risk of abuse potential is low. Thus, no withdrawal/rebound effects or abuse potential will be presented in the submission. Does the Division agree with Amarin's plan?

FDA Preliminary Response: Although you have no specific trials to test for drug abuse potential, you should plan to submit documentation stating any prior history of drug abuse potential or withdrawal with other members of AMR101 pharmacological class of drugs. Reports of significant overdose in post-marketing data from other countries should be submitted. You should also submit directives for overdose measures.

Meeting Discussion: In response to a question from the firm, the agency clarified that drug abuse potential or withdrawal documentation should pertain to the pharmacological class of drugs (fish oil products) approved by a regulatory body in Japan, Europe, or the US.

CL-10 Amarin plans to provide analyses on special topics of the FDA requested possible drug related hepatic disorders and severe cutaneous adverse events in the integrated safety summary. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-11 Amarin proposes the definitions shown in the following table for potentially clinically significant (PCS) laboratory values. Does the Division agree with the proposed PCS laboratory criteria?

Potentially Clinically Significant Chemistry Values

Parameter	PCS Low	PCS High
Albumin	<3.3 g/dL	>5.8 g/dL
Alkaline Phosphatase	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN

Parameter	PCS Low	PCS High
		>3x ULN
ALT	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
AST	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
Bilirubin	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT + Bilirubin	NA	>3x ULN (ALT) + 2 x ULN (Bilirubin)
AST + Bilirubin	NA	>3x ULN (AST) + 2x ULN (Bilirubin)
Calcium	≤7 mg/dL	≥12 mg/dL
Creatinine	<0.5 mg/dL (Female) <0.65 mg/dL (Male)	≥1.6 mg/dL (Female) ≥2.0 mg/dL (Male)
Creatinine Kinase		≥1xULN to 5xULN ≥5xULN to 10xULN ≥10xULN
Glucose (fasting)	≤36 mg/dL	≥130 mg/dL
Magnesium	<1.5 mg/dL	≥2.7 mg/dL
Potassium (K)	≤3.0 mEq/L	≥5.5 mEq/L
Sodium (Na)	≤130 mEq/L	≥150 mEq/L
Total Protein	<5.0 g/dL	≥9.5 g/dL
Urea nitrogen (BUN)	NA	≥31 mg/dL

Note: values are given in terms of Conventional units Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; g/dL = grams per deciliter; Eq/L = milliequivalents per liter; mg/dL = milligrams per deciliter; NA = Not applicable; PCS = potentially clinically significant, ULN = upper limit of normal.

Potentially Clinically Significant Hematology Values

Parameter	PCS Low	PCS High
Hemoglobin (Hb)	≤10.0 g/dL (Female) ≤10.0 g/dL (Male)	≥16.5 g/dL ≥18.0 g/dL
Red Blood Cells (RBC)	≤3.5 X 10 ⁶ /μL (Female) ≤3.8 X 10 ⁶ /μL (Male)	>5.5 X 10 ⁶ /μL (Female) >6.0 X 10 ⁶ /μL (Male)
White Blood Cells (WBC)	≤1.5 X 10 ³ /μL	NA

Parameter	PCS Low	PCS High
Platelet count	$\leq 100 \times 10^3/\mu\text{L}$	$\geq 500 \times 10^3/\mu\text{L}$

Note: values are given in terms of SI units

Abbreviations: g/dL = grams per deciliter; NA = Not Applicable; PCS = potentially clinically significant; μL = microliter

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-12 Amarin proposes the definitions shown in the following tables for change from baseline categories (i.e. shift) and potentially clinically significant (PCS) vital signs values. Does the Division agree with the proposed change from baseline and PCS vital sign criteria? Supine positions if available and alternatively, sitting positions will be used. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

Vital Signs Value Categories (Change from Baseline Categories)

Vital Sign	Low	Normal	High
Systolic Blood Pressure	≤ 90 mmHg	>90 mmHg- <160 mmHg	≥ 160 mmHg
Diastolic Blood Pressure	≤ 50 mmHg	>50 mmHg- <100 mmHg	≥ 100 mmHg
Pulse	≤ 50 beats/min	>50 beats/min- <90 beat/min	≥ 90 beats/min

Potentially Clinically Significant Vital Signs Value Definitions

Vital Sign	PCS Low	PCS High
Systolic Blood Pressure	≤ 90 mmHg AND decrease of ≥ 20 mmHg	≥ 160 mmHg AND increase of ≥ 20 mmHg
Diastolic Blood Pressure	≤ 50 mmHg AND decrease of >10 mmHg	≥ 100 mmHg AND increase of >10 mmHg
Pulse	≤ 50 beats/min AND decrease of ≥ 15 beats/min	≥ 90 beats/min AND increase of ≥ 15 beats/min

CL-13 Amarin proposes that the Clinical Safety Summary in Module 2 will comprise the front matter from the Integrated Summary of Safety contained within 5.2.5.2. Does the FDA agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-14 Amarin plans on submitting CDISC SDTM datasets based upon the implementation guide 3.1.2 and ADaM datasets based upon the implementation guide 1.0. These datasets will be submitted as Version 5 SAS transport format (SAS Xport). Does the Division agree with this approach?

FDA Preliminary Response: This appears acceptable.

Meeting Discussion: None

CL-15 Amarin will be using a single version of MedDRA for the Hypertriglyceridemia studies, the ISS data and ISS analysis. Other indications were re-mapped from the raw datasets to the updated MedDRA version. The clinical study reports and individual study datasets for the CNS studies will not be submitted in this submission. Therefore, it is not necessary to provide a list of events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another version. Does the Division agree with this approach?

FDA Preliminary Response: Clarify why the CNS studies will not be submitted.

Meeting Discussion: The following agreements were reached:

- The individual study datasets from the CNS trials would NOT be submitted. However, the sections of the CNS study reports pertaining to safety will be provided in Module 5.
- Safety data from the CNS trials will be provided in the integrated summary of safety database and reports
- Narratives and Case Report Forms from the CNS trials for the appropriate patients will be provided

CL-16 The 120-day safety update will include information regarding any treatment emergent SAEs observed in ongoing studies (MARINE open label and REDUCE-IT). There is no plan to further integrate data or provide additional clinical data at that time. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

REGULATORY (RA)

NOTE- We have not responded to most of the labeling questions below. The final label will be negotiated following review of the application.

RA-1 Given the significant improvement demonstrated in the MARINE study, of eliminating the treatment-limiting drug reaction of substantial increases in LDL-C over the approved products, Amarin asserts that on this basis and in accordance with FDA MAPP 6020.3 - PRIORITY REVIEW POLICY, a review classification of P -- Priority review should be assigned to the NDA application. Does the FDA agree that this application will qualify for priority review?

FDA Preliminary Response: A determination as to whether the application will be designated for a Standard or Priority review will be made by the filing date (60 days following receipt of the application).

Meeting Discussion: The firm pressed for a more definitive response given the limited resources of the company. The sponsor was informed that there was a higher probability that the application would be reviewed under a Standard review timeline than under a Priority review timeline.

RA-2 Based upon the results of the MARINE clinical study and the factors set forth in section III.A.1 of the FDA's August 2008 Guidance on Convening Advisory Committee Meetings, AMR101 is not likely to be referred for Advisory Committee review. Does the FDA agree?

FDA Preliminary Response: Under 505(s) of the FD&C Act, all new chemical entities must either be discussed at an Advisory Committee Meeting or a justification provided as to why it will not be discussed. A final decision on whether AMR101 is a new chemical entity has not been made.

Meeting Discussion: The firm pressed for a more definitive response given the limited resources of the company. The sponsor was informed that, based on what is known about the compound at this time, and in our opinion it was less likely that AMR101 would go to an Advisory Committee. Final decision on the question of an Advisory Committee would be made after submission of the NDA.

RA-3 Amarin proposes to display, in tabular format, adverse events from the MARINE study only in the Adverse Event section. Does the FDA agree with this approach?

RA-4 Amarin proposes to display in the table of adverse events, from the MARINE study, all those events that occurred at a rate of >3% (i.e., in more than 2 patients) in any treatment group. Does the FDA agree that this is acceptable?

FDA Preliminary Response: This is acceptable. However, the events must also occur at a rate more often in subject taking drug than in subjects taking placebo.

Meeting Discussion: In response to a question from the firm, the agency clarified that we were asking for adverse events from that single study, not from the integrated report.

Post-Meeting Discussion- We request that you provide the adverse reaction data both from the single MARINE trial and from the pooled integrated summary of safety data (two tables).

RA-5 Amarin proposes to describe the adverse events for the Integrated Dataset, including the ANCHOR study and CNS studies, in paragraph form below the adverse event table. Does the FDA agree with this approach?

RA-6 Amarin proposes to describe adverse events, from the Integrated Dataset in the text, that are >5% in the AMR101 treated patients. Does the FDA agree with this approach?

RA-7 Amarin proposes to describe adverse events from the Integrated Safety Database that occurred in special populations, such as diabetics and patients concomitantly treated with statins, in text below the adverse event table. This information is important for physicians in determining whether or not treatment with AMR101 is appropriate for these patients. Potential text may be as follows. Does the FDA agree with this approach?

X### patients have received statin treatment concurrent with AMR101 treatment. The incidence of adverse events for patients on statins plus AMR101 was not different from patients treated with AMR101 alone.

X### patients with diabetes mellitus have been treated with AMR101. The safety profile for patients with diabetes mellitus is similar to non-diabetics.

RA-8 Within the package insert where the pivotal clinical study will be described, Amarin proposes to display results in graphical format (see example above) in order to most effectively communicate the effects and differences across dose groups. Does the FDA agree with this approach?

Meeting Discussion: The agency is not opposed to data being presented in graphical format.

RA-9 Amarin proposes that the endpoints displayed in the graphical example will be the endpoint data that are displayed from the MARINE study as it is the most relevant to a physician's prescribing decision for use of the drug. Does the FDA agree with this approach?

RA-10 Additional endpoints that were measured in the clinical study will be briefly described in paragraph format below the efficacy data graph as shown in the sample text below.

AMR101 4 grams per day significantly reduced LDL particle number (p=0.0042), remnant-like particle cholesterol (p=0.0041), hs-CRP (p=0.0012), Apo A1 (p=0.009), and the AA/EPA ratio from baseline relative to placebo.

Does the FDA agree with this approach?

RA-12 Does the FDA have any additional comments or guidance regarding the preparation of the draft package insert?

FDA Preliminary Response: No.

Meeting Discussion: None

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

Division of Scientific Investigations (DSI) documents pertaining to the future NDA submission

DSI Comments for the preNDA meeting IND 102,457
Product: AMR101 Capsules
Sponsor: Amarin Pharma, Inc.
From: Susan Leibenhaut, M.D., GCPB II/DSI/OC

DSI has 2 types of requests for data to be submitted to the NDA; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

I. Request for general study related information and specific Clinical Investigator information

A. Please include the following information in a tabular format in the original NDA for the completed Phase 3 clinical trial MARINE, AMR-01-01-0016:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for the completed Phase 3 clinical trial:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for the completed Phase 3 clinical trial:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

II. Request for Site Level Data

1. For each site in the pivotal clinical trial: Name of primary investigator, accurate address and phone number, e-mail contact.
2. For the pivotal trial: Sample blank CRF and case report data tabulations for the site with coding key.
3. For the pivotal trial: Site-specific individual subject data (“line”) listings from the datasets:
 - a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements

- b. Line listings by site and subject, of treatment assignment (randomization)
- c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
- d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
- e. Line listings by site and subject, of AEs, SAEs, deaths and dates
- f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
- h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
- i. Line listings by site and by subject, of laboratory tests performed for safety monitoring

III. Request for Individual Patient Data Listings format:

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

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

I. INTRODUCTION

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

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

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

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

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

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

Site-Specific Efficacy Results

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

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

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

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

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

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

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

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

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

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

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Summary Level Clinical Site Data Elements

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

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

Exhibit 2: General Structure of Data Submission Template

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLDISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

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

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/s/

KATI JOHNSON
03/23/2011