

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BL 125249/0

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 125249 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

App Date: May 29, 2007 PDUFA Goal Date: November 29, 2007

HFD 170 Trade and generic names/dosage form: Arcalyst (IL-1 Trap)

Applicant: Regeneron Pharmaceuticals Therapeutic Class: _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next section.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into RMS-BLA Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies waived.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Partially Waived

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Deferred

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

Where there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered in RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Data Submitted and Complete.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager



FEB 5 2008

cc: BLA 125249/0
Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT ROSEMARY ADDY OR GRACE CARMOUZE

(revised for TBP licensing products 9-15-2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
 NOTE: More than one may apply
 Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into RMS-BLA Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Waived.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - SummaryText: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Partially Waived.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Adult studies ready for approval
 Formulation needed
 Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - SummaryText: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Deferred.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - SummaryText: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Data Submitted and Complete.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: BLA 125249/0
Rosemary Addy or Grace Carmouze

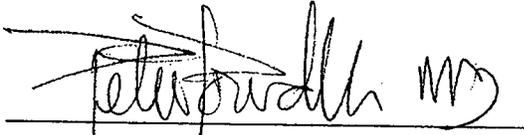
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT ROSEMARY ADDY OR GRACE CARMOUZE

(revised for TBP licensing products 9-15-2006)

1.3.3 Debarment Certification

1.3.3 Debarment Certification

Regeneron Pharmaceuticals, Inc. 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.



Peter Powchik
Senior VP and Head, Clinical Development
777 Old Saw Mill River Road
Tarrytown, NY 10591

02 Feb 2007

Date

ACTION PACKAGE CHECKLIST

Application Information		
BLA # 125249 NDA #	BLA STN# 125249/0 NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Arcalyst Established Name: Rilonacept (IL-1 Trap) Dosage Form: 160 mg/vial (for reconstitution) subcutaneous injection		Applicant: Regeneron Pharmaceuticals
RPM: Kathleen Davies		Division: 170 Phone # 301-796-2205
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
(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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain:
		Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.
<input type="checkbox"/> Confirmed		<input type="checkbox"/> Corrected
Date:		
❖ User Fee Goal Date		February 27, 2008
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed
Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		

Application Characteristics

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

NDAs, BLAs and Supplements:

- Fast Track
- Rolling Review
- CMA Pilot 1
- CMA Pilot 2

Orphan drug designation

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

NDAs and NDA Supplements:

- OTC drug

Other:

Other comments:

Application Integrity Policy (AIP)

• Applicant is on the AIP

- Yes No

• This application is on the AIP

- Yes No

- Exception for review (*file Center Director's memo in Administrative Documents section*)
- OC clearance for approval (*file communication in Administrative Documents section*)

- Yes No

- Yes Not an AP action

Public communications (approvals only)

• Office of Executive Programs (OEP) liaison has been notified of action

- Yes No

• Press Office notified of action

- Yes No

• Indicate what types (if any) of information dissemination are anticipated

- None
- FDA Press Release
- FDA Talk Paper
- CDER Q&As
- Other

notice of certification?

(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 to the next section below (Summary Reviews).

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

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p>Summary Reviews</p>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>CDTL Review 12/17/07; DD Review 2/8/08</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	<p>2/27/08</p>
<p>Labeling</p>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>x</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>x</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>x</p>
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>x</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>x</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>x</p>
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	<p>N/A</p>
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	<p>x</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>x</p>
<p>❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)</p>	<p><input checked="" type="checkbox"/> DMETS 11/16/07, 2/27/08</p> <p><input checked="" type="checkbox"/> DSRCS 2/25/08</p> <p><input checked="" type="checkbox"/> DDMAC 10/23/07</p> <p><input type="checkbox"/> Other reviews</p> <p><input type="checkbox"/> Memos of Mtgs</p>

Administrative Dispositions	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (indicate date of each review)	June 21, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (Include certification.)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (if located elsewhere in package, state where located) 	X
<ul style="list-style-type: none"> • Incoming submission documenting commitment 	February 27, 2008
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	x
❖ Internal memoranda, telecons, email, etc.	x
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (indicate date; approvals only) 	10/18/07
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (indicate date) 	<input type="checkbox"/> No mtg September 19, 2006, December 12, 2006 (Product only)
<ul style="list-style-type: none"> • EOP2 meeting (indicate date) 	<input type="checkbox"/> No mtg February 16, 2006
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	Type A November 28, 2007
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date of Meeting • 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Other Quality Information	
❖ CMC/Product review(s) (indicate date for each review)	2/27/08, 2/27/08 (TL)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> • <input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population) 	In product review
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & FONSI (indicate date of review) • <input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (indicate date of each review)	
❖ Facilities Review/Inspection	<input type="checkbox"/> Not a parenteral product
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) 	Date completed: December 6, 2007, <input checked="" type="checkbox"/> Acceptable

	<input type="checkbox"/> Withhold recommendation
--	--

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review <i>(indicate date(s))</i> • Compliance Status Check (approvals only, both original and supplemental applications) <i>(indicate date completed, must be within 60 days prior to AP)</i> 	<input type="checkbox"/> Requested <input checked="" type="checkbox"/> Accepted January 22, 2008 <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	January 18, 2008, December 19, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

Clinical Information

Clinical review(s) <i>(indicate date for each review)</i>	December 18, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	In clinical review.
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	N/A
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	October 29, 2007
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested
• Clinical Studies	October 22, 2007
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 18, 2007
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 20, 2007

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

LICENSING ACTION RECOMMENDATION
(Required for all BLA supplements without a Completion Package)

Applicant: Regeneron Pharmaceuticals BLA #: 125249

Product (established and proprietary names):

Arcalyst (rilonacept)

Indication / Requested change:

Treatment of CAPS

RECOMMENDED ACTION

Approval:

Refusal to File:

Denial of application / supplement:

RECOMMENDATION BASIS
(Select all that apply)

- Refusal to File Memo
- Denial of Application/Supplement Memo

- Approval Action - Discipline Reviews
- Approval Action - 2^o Review
- Approval Action - 3^o Review

- Review of labeling
 - Package Insert - Content
 - Package Insert - SPL Data Elements
 - Package Insert - PLR Format
 - Patient Package Insert
 - Medication Guide
 - Container / Carton (OBP review)

DMPQ Establishment inspections completed

DSI BiMo Inspections completed

OBP Review of Protocols for lot no.(s) _____

OBP Review of Test Results for lot no.(s) _____

Review of Environmental Assessment

FONSI included

Categorical Exclusion

CLEARANCE - FDA PRODUCT RELEASE Required for Non-Specified Products Only
<input type="checkbox"/> Lot no.(s) in support - not for release _____
<input type="checkbox"/> Lot no.(s) for release _____
Director, Product Release Branch _____

N/A

CLEARANCE - REGULATORY REVIEW

Compliance status checked - Acceptable

Compliance status checked - Hold (Requires justification for approval action)

Compliance status check not required (CBE Labeling supplements ONLY)

Regulatory Project Manager (RPM) *K. Williams*

Date: 27 Feb 08

Chief, Project Management (CPMS) *Sara Estroffley*

Date: 2-27-08

FINAL CLEARANCE

Cross-Discipline Team Leader (if assigned) *Jeffrey H. Neel*

Date: 2/27/08

Responsible Division Director _____

Date: 2/27/08

ADRA Rev #1 of Action Package for BLA 125490

Reviewer: Lee Ripper, HFD-102
Date received: 2/7/08
Date of review: 2/8/08; 2/27/08
Date original BLA received: 5/29/07
UF goal date: 2/27/09

Lee Ripper
2/27/08

Proposed Indication: _____ treatment, _____ of
Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold
Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)

Action type: AP

RPM: Kathleen Davies

Drug Classification: 1PV

Debarment Certification: AC

Financial Disclosure: 1 covered clinical study, no reported financial interests

Safety Update: MOR, page 66

Statistics Review: 12/18/07, see labeling comments pages 17-18.

Clinical Pharmacology Review: 12/20/07, no PMCs, labeling comments page 31-34.

OSE Review of Risk Management Plan: 10/29/07, no formal RiskMAP, see Recommendations
on labeling _____

Clinical Inspection Summary: 4 clinical sites audited; data appear acceptable for use in support
of the BLA.

ODS/DMETS Review of Proprietary Name: DMETS and DDMAC found proprietary name
acceptable. Review signed 11/16/07; email RPM 2/12/08 to request followup
proprietary name review. *CM 2/26/08*

DRISK Review of PPI: 2/22/08

DDMAC Review: 10/23/07 review of PI, PPI, and carton and container labeling; 2/26/08.

SEALD/MHT Review of PLR: 2/12/08

EA: Categorical Exclusion, last page of the Quality TL Executive Summary

EER: Acceptable 1/23/08

PSC/WU Mtg: 10/30/07; RPM to draft memo to file re: PSC

OBP review in draft as of 2/8.

P/T tertiary review by David Jacobson-Kram; *completed 2/21/08.*

1. 2/12/08: Requested

Copies of ACK and 60-day letters – *rec'd*

Status of minutes of PSC mtg – *see 2/27 memo from RPM*

Has DRISK reviewed the PPI – *2/22/08*

Has SEALD reviewed the PI – *2/13/08*

What is the status of the final CMC review and the TL Exec Summary – *2/26/08*

What is status of DMETS follow-up review of proprietary name – *2/26/08*

Pages 87-169 of P/T review are missing – *replaced*

REGENERON

REGENERON PHARMACEUTICALS, INC.
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591-6707
TELEPHONE: 914-345-7590
FACSIMILE: 914-345-7688
E-MAIL: mierette.stocker@regeneron.com

Mierette R. Stocker
Director, Regulatory Affairs

February 27, 2008

Dr. Bob Rappaport
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologics Products
Document Room 5901-B
Ammendale Road Beltsville, MD 20705-1266

Attention: Ms. Kathleen Davies
Regulatory Project Manager

Re: Biologics License Application Number STN 125249
Regeneron Pharmaceuticals, Inc.
Riloncept
Final response to post-marketing commitments

Dear Dr. Rappaport:

Please refer to Biologics License Application (BLA) number 125249 for ARCALYST (riloncept) for the treatment of cryopyrin-associated periodic syndrome (CAPS). Please be advised that Regeneron agrees to the post-marketing commitments as described in Attachment 1.

Should there be any questions, please do not hesitate to call me at 914-345-7590. In the event that I cannot be reached and the Agency has a concern that requires immediate attention, you may contact Dr. William Roberts at 914-345-7940.

Sincerely,

Mierette R. Stocker
Director, Regulatory Affairs

7 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]

Sent: Wednesday, February 27, 2008 2:34 PM

FEB 27 2008

To: Davies, Kathleen

Km Davies

Subject: Final post-marketing commitments - BLA 125249

Attachments: postmarketing commitments_REGN response_FINAL_080227.doc; postmarketing commitments_REGN response_FINAL_080227.pdf; emfinfo.txt

Dear Kathleen,

Please find enclosed our agreement to the final post-marketing commitments. I am also providing the word document incase you need it.

I have changed CMC #4

_____ as we discussed this morning.

I believe that I have provided all that you need. If you have any questions, please call my cell phone (914-548-4390).

Many thanks,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

Davies, Kathleen

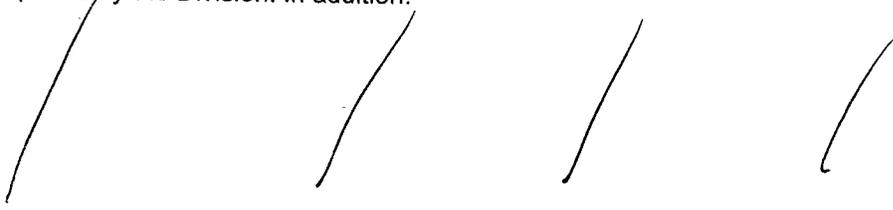
From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Wednesday, February 27, 2008 2:10 PM
To: Davies, Kathleen
Subject: Final Patient Information Leaflet for Arcalyst
Attachments: ARCALYST PPI_FINAL_with TC_080227.doc; ARCALYST PPI_FINAL_clean_080227.doc; ARCALYST PPI_FINAL_clean_080227.pdf; emfinfo.txt

FEB 27 2008

Km Davies

Dear Kathleen,

Please find enclosed the final patient information leaflet for Arcalyst. We have accepted the final changes proposed by the Division. In addition:



These changes are apparent in the enclosed word document with the filename: ARCALYST PPI_FINAL_with TC_080227

I am also enclosing clean Word and pdf documents (filename: ARCALYST PPI_FINAL_clean_080227). I will be sending the final PMCs very shortly.

Thanks,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com] FEB 27 2008
Sent: Wednesday, February 27, 2008 1:54 PM
To: Davies, Kathleen
Subject: RE: Carton/container comments and PPI comments
Attachments: 1112 ArcalystCarton-RV2-4.pdf; 1112 ArcalystLbi-RV2-4.pdf; emfinfo.txt

Dear Kathleen,

Please find enclosed mock-ups of the vial and carton labels that indicate the placement and format of the lot number and expiration date.

Please let me know if you have questions.

Kind regards,

Mierette

O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Tuesday, February 26, 2008 5:35 PM
To: Mierette Stocker
Subject: Carton/container comments and PPI comments

Hi Mierette,

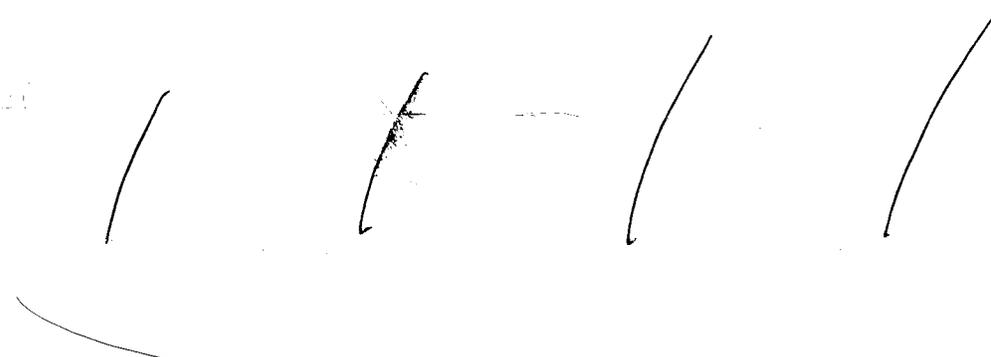
Please refer to BL 125249 for Arcalyst. We have the following follow-up comments regarding the carton/container labels:

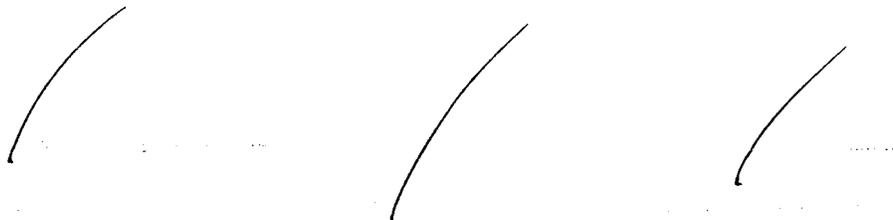
Include lot number and expiration date on the container label according to 21 CFR 610.60 (3) and (4).

Include lot number and expiration date on the carton label according to 21 CFR 610.61 (c) and (d).

With regard to the PPI, I have attached a track-changes version of your PPI you sent. This was re-reviewed by DRISK and they had some follow up comments. To briefly highlight them for you (there are additional changes not mentioned here as well):

2/27/2008





We will wait for your immunogenicity information to send a final PI for concurrence.

Kathleen

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Wednesday, February 27, 2008 1:48 PM
To: Davies, Kathleen
Subject: Final FPI for ARCALYST
Attachments: ARCALYST FPI_final_clean_080227.pdf; ARCALYST FPI_final_clean_080227.doc; emfinfo.txt

FEB 27 2008

Km Davies

Dear Kathleen,

We have accepted the final changes proposed by the Division. Please find enclosed the final full prescribing information for Arcalyst, which I am providing as Word and pdf documents.

I will be sending the remaining items very shortly.

Kind regards,

Mierette

O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Wednesday, February 27, 2008 12:14 PM
To: Mierette Stocker
Subject: RE: Final PI for concurrence

Hi Mierette,

The carton and containers are acceptable as is.

We will wait for your carton/container mock up, new PPI, agreement on the PI and your PMCs. Please provide them as soon as possible.

Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Wednesday, February 27, 2008 12:04 PM
To: Davies, Kathleen
Subject: RE: Final PI for concurrence

Thank you – we are reviewing now and plan to send you the final very shortly.

Do you know when you will have the remaining comments regarding these labels?

Thanks

2/27/2008

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

Sent: Wednesday, February 27, 2008 11:34 AM

To: Mierette Stocker

Subject: Final PI for concurrence

Importance: High

Hi Mierette,

Please find the final PI for your review/concurrence.

Please review and let me know if Regeneron accepts this PI.

Kathleen

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Tuesday, February 26, 2008 5:22 PM
To: Davies, Kathleen
Subject: RE: BLA 125249 Revised PI
Attachments: ARCALYST pediatric dosing chart_option 2 for 7-17_final_080226_for submission.doc; emfinfo.txt

Km Davies
FEB 27 2008

Dear Kathleen,

Please see enclosed document which contains a proposal for _____
I am providing as a word document in the event the Division agrees and would like to insert into the label.

Please let me know if you have any questions.

Thanks,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Monday, February 25, 2008 10:58 PM
To: Mierette Stocker
Subject: RE: BLA 125249 Revised PI

Hi Mierette,

Please provide a _____

Thanks,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Fri 2/22/2008 6:08 PM
To: Davies, Kathleen
Subject: BLA 125249 Revised PI

Dear Kathleen,

Please see revised PI enclosed. I have accepted all the agreed upon changes. Changes made subsequent to our teleconference yesterday are highlighted in yellow. I have also enclosed supporting documents for the _____ and the immunogenicity section of the label as requested.

We will be reviewing FDA's changes to the patient leaflet and plan to give you our feedback on Monday.

Have a nice weekend,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

2/27/2008

(B)

 1 Page(s) Withheld

 Trade Secret / Confidential

 J Draft Labeling

 Deliberative Process

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Tuesday, February 26, 2008 5:19 PM
To: Davies, Kathleen
Subject: RE: PMC clarification to Clinical #2
Attachments: postmarketing commitments_REGN response_080226.doc; emfinfo.txt

FEB 27 2008

KMDavies

Dear Kathleen,

We find the proposal below acceptable and I have incorporated it into the PMC response document which is enclosed.

Kind regards,

Mierette

O: 914-345-7590

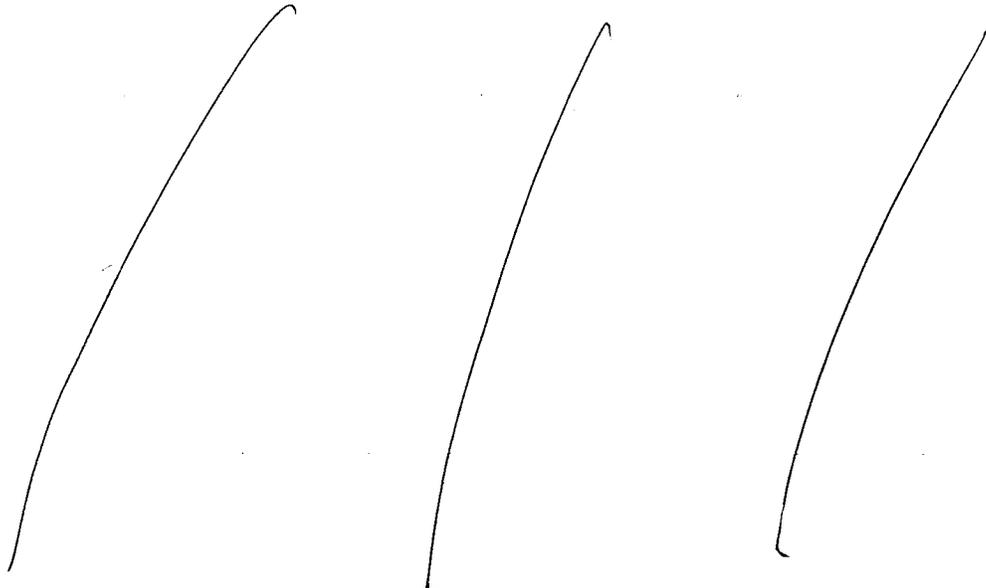
M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Tuesday, February 26, 2008 4:02 PM
To: Mierette Stocker
Subject: PMC clarification to Clinical #2
Importance: High

Hi Mierette,

Please refer to the PMC teleconference today. The Clinical Team Leader, Dr. Siegel, offers the following proposal for PMC #2 Clinical:



Please review and let me know if this is acceptable. In addition, please send all of the PMCs and your agreed upon commitments to me via email today. I will give it to the team to review and concur/propose alternatives.

Attendees:

Bob Rappaport, MD, Director

Rigoberto Roca, MD, Deputy Director

Jeff Siegel, MD, Clinical Team Leader

Keith Burkhardt, MD, Clinical Reviewer

Chana Fuchs, PhD, Product Team Leader, DMA

Ruth Cordoba, PhD, Product Reviewer, DMA

Jun Park, PhD, Product Reviewer, DMA

Lei Zhang, PhD, Clinical Pharmacology Reviewer

Hao Zhu, PhD, Clinical Pharmacology Reviewer

Bo Chi, PhD, Facilities reviewer, DMPQ

Kathleen Davies, MS, Regulatory Health Project Manager

On another note, I will send comments regarding the carton and container and PPI shortly for your review.

We are waiting for your immunogenicity data for the PI.

Thanks,

Kathleen



1

7 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

FDA clarification:

Does the calculation include all patients who received P4B? This should include those patients who initially received P4A during the single blind phase and then P4B during the open label extension, given that the P4A and P4B products were found to be biochemically and biologically comparable.

Regeneration response:

- Yes, the calculation includes all patients who received P4B, regardless of whether they received P4A previously. Hence, regardless of prior therapy with P4A, patients received P4B if:
 - The subject was randomized to receive rilonacept during the randomized withdrawal (RW) portion of the study
 - The subject entered into the 24-week open label extension (OLE) phase.
- A subject is counted as antibody positive only if a sample was positive during treatment with P4B rilonacept.

Please see overview of subjects in the pivotal study IL1T-AI-0505 in CAPS who were positive in the BA3 antibody assay after at least 6 weeks of treatment with P4B rilonacept on the next page:

Proposed language for prescribing information:

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 subjects (35%) who had received ARCALYST for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19, seven tested positive at the last assessment, and five subjects tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety.

Subjects with positive anti-rilonacept antibody assessment during treatment with P4B rilonacept during the pivotal study IL1T-AI-0505 in CAPS (BA3 assay [directed against IL-1 receptor extracellular domain components], unless noted otherwise)

Subject cohort	Number of subjects in cohort	Subjects with treatment emergent positive anti-rilonacept antibody assessments during treatment with P4B rilonacept	Comments
<p>Subjects who received P4B rilonacept for at least 6 weeks during either the 24-week open label extension phase or the randomized withdrawal:</p> <p>(a) those who entered the study directly into the 24-week open label extension phase (see above) plus</p> <p>(b): those who entered Part B of the study and received P4B rilonacept during the randomized withdrawal phase and/or in the subsequent 24-week open label extension after completing the RW</p>	<p>56</p> <p>(a) 12 subjects</p> <p>(b) 44 subjects (Note: this does not include subject 029-6529, who terminated early during the Part B administration of P4B rilonacept; this subject had an antibody assessment performed [negative] at the early termination visit 7 weeks after the administration)</p>	<p>19 of 55 (35%)</p> <p>(a) n=1</p> <p>007-8007, during OLE ♦</p> <p>(b) n=18</p> <p>002-6492, during OLE</p> <p>003-6192, during OLE</p> <p>004-6256, during OLE</p> <p>004-6983, during RW and OLE</p> <p>007-6482, during OLE ♦</p> <p>009-6025, during RW and OLE ♦</p> <p>015-6995, during RW</p> <p>016-6238, during OLE</p> <p>016-6277, during RW</p> <p>020-6566, during RW and OLE</p> <p>021-6003, during RW</p> <p>025-6906, during RW and OLE ♦</p> <p>029-6814, during OLE ♦</p> <p>(ref SAR IL1T_AI_0505_SA_02V1, section 6.5, and Appendix 10, Table 9, and SAR IL1T_AI_0505_SA_01V2, sections 6.1.5 and 6.3.5, and Appendix Tables 6 and 18)</p>	<p>(a) In the previous column, treatment-emergent antibody positive for P4B does not include subject 007-8002 who was antibody positive on OLE study day 0, prior to initial dosing (ref SAR IL1T_AI_0505_SA_02V1, section 6.5, p. 20, lines 8 to 11, and Appendix 10, p 47, last portion of Table 9)</p> <p>(b) Subjects 002-6824, 007-6875, and 015-6301 are not counted as antibody positive because a positive assessment did not occur after exposure to P4B rilonacept, only during treatment with P4A. It is noteworthy that one of these three subjects, 015-6301, also tested antibody-positive at baseline prior to any treatment with rilonacept.</p>

RW, randomized withdrawal; OLE, open label extension; subjects with a positive BA3 assay at the last assessment during treatment with P4B rilonacept are indicated with a red diamond ♦, and subjects with a positive neutralizing Ab during treatment with P4B are shown with [redacted].

References: SAR IL1T_AI_0505_SA_01V2 (re Parts A and B of the IL1T-AI-0505 study); SAR IL1T_AI_0505_SA_02V1 (re 24-week open label extension phase of the IL1T-AI-0505 study)

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Monday, February 25, 2008 6:48 PM
To: Davies, Kathleen
Subject: RE: BLA 125249/Arcalyst - PPI for review and consideration
Attachments: Arcalyst PPI_FDA proposed_REGN edits 25Feb08_with figures.doc; emfinfo.txt

FEB 27 2008
Km Davies

Hello Kathleen,

Please find enclosed the revised PPI, this time with the figures inserted. Please forward to the appropriate reviewers.

Thanks and kind regards,

Mierette

O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

From: Mierette Stocker
Sent: Monday, February 25, 2008 10:56 AM
To: Davies, Kathleen
Subject: RE: BLA 125249/Arcalyst - PPI for review and consideration

Good morning Kathleen,

Please find enclosed the revised PPI. We have reviewed and addressed the comments from the division. The figures are being rendered today, so there are placeholders for each figure for now. I hope to resend the document with the new figures late today or first thing tomorrow morning.

Please let me know if you have any questions.

Thanks,

Mierette

O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, February 22, 2008 3:36 PM
To: Mierette Stocker
Subject: BLA 125249/Arcalyst - PPI for review and consideration
Importance: High

Hi Mierette,

Please refer to BL 125249 for Arcalyst. We have completed our review of the PPI & I have attached a pdf version of our tracked changes and a clean word version. Highlighted sections are either notes to you on why something was done or a request from the division of risk management.

Please review and provide feedback on this label as soon as possible but no later than COB Monday.

Thanks,

Kathleen

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Monday, February 25, 2008 10:56 AM
To: Davies, Kathleen
Subject: RE: BLA 125249/Arcalyst - PPI for review and consideration
Attachments: Arcalyst PPI_FDA proposed_REGN edits 24Feb08.doc; emfinfo.txt

FEB 25 2008

Km Davies

Good morning Kathleen,

Please find enclosed the revised PPI. We have reviewed and addressed the comments from the division. The figures are being rendered today, so there are placeholders for each figure for now. I hope to resend the document with the new figures late today or first thing tomorrow morning.

Please let me know if you have any questions.

Thanks,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, February 22, 2008 3:36 PM
From: Mierette Stocker
Subject: BLA 125249/Arcalyst - PPI for review and consideration
Importance: High

Hi Mierette,

Please refer to BL 125249 for Arcalyst. We have completed our review of the PPI and I have attached a pdf version of our tracked changes and a clean word version. Highlighted sections are either notes to you on why something was done or a request from the division of risk management.

Please review and provide feedback on this label as soon as possible but no later than COB Monday.

Thanks,

Kathleen

2/25/2008

Davies, Kathleen

FEB 25 2008



From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Friday, February 22, 2008 6:08 PM
To: Davies, Kathleen
Subject: BLA 125249 Revised PI
Attachments: ARCALYST pediatric dosing chart.pdf; Immunogenicity of rilonacept with P4B drug product_final.pdf; PI_REGN 22Feb08.doc; emfinfo.txt

Dear Kathleen,

Please see revised PI enclosed. I have accepted all the agreed upon changes. Changes made subsequent to our teleconference yesterday are highlighted in yellow. I have also enclosed supporting documents for the _____ and the immunogenicity section of the label as requested.

We will be reviewing FDA's changes to the patient leaflet and plan to give you our feedback on Monday.

Have a nice weekend,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Friday, February 22, 2008 4:44 PM
To: Davies, Kathleen
Subject: BLA 125249 Post-marketing commitments
Attachments: postmarketing commitments_draft REGN response.pdf

FEB 25 2008

KM Stocker

Dear Kathleen,

Please find enclosed our draft responses to the proposed post-marketing commitments, which we can use to facilitate our discussions.

Kind regards,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

2/25/2008

8 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, February 22, 2008 3:36 PM
To: 'Mierette Stocker'
Subject: BLA 125249/Arcalyst - PPI for review and consideration
Importance: High
Attachments: Arcalyst PPI_FDA proposed.pdf; Arcalyst PPI_FDA proposed_clean.doc

FEB 25 2008

K. Davies

Hi Mierette,

Please refer to BL 125249 for Arcalyst. We have completed our review of the PPI and I have attached a pdf version of our tracked changes and a clean word version. Highlighted sections are either notes to you on why something was done or a request from the division of risk management.

Please review and provide feedback on this label as soon as possible but no later than COB Monday.

Thanks,

Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, February 22, 2008 12:18 PM
To: 'Mierette Stocker'
Subject: RE: BLA 125249 Revised container and carton labels

FEB 25 2008

K. Davies

Hi Mierette,

The license number cannot be provided ahead of time because it is linked to approval. If our final decision is to approve your application, the license number will be clearly stated in the approval letter.

Thanks,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Wednesday, February 20, 2008 3:37 PM
To: Davies, Kathleen
Subject: BLA 125249 Revised container and carton labels

Dear Kathleen,

Please find enclosed revised carton and container labels, which we believe addresses FDA concerns. Please forward to the appropriate reviewers.

I would like to inquire about the availability of the license number that is required to appear on the vial and carton label. Since this is our first BLA, we are uncertain of when the license number is assigned. Can you clarify if the license number can be provided ahead of time (assuming that the final activities related to the BLA review continue to move ahead in an encouraging direction) so we can begin printing at risk? If we receive positive feedback on the vial and carton labels, we would like to begin the printing process, which will not be possible without the license number. Please understand that we are not trying to be presumptive regarding product approval. We are trying to build timelines for when commercial product can be made available to patients, if the product were to be approved. Any information you can provide will be helpful.

Please let me know if you have any questions.

Kind regards,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, February 22, 2008 9:50 AM
To: 'Mierette Stocker'
Subject: BL 125249/Arcalyst - PI
Importance: High
Attachments: PI_Regn 080219_FDA edits 21Feb08.doc; PI_Regn 080219_FDA edits 21Feb08.pdf

FEB 25 2008

Km Davies

Hi Mierette,

Please find the PI per our discussions yesterday attached. If you note any discrepancies, please let me know.

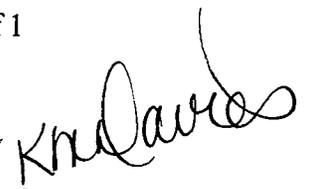
The team is working on the PPI and I hope to have that you to later this afternoon.

If you have any questions, let me know.

Regards,

Kathleen

Davies, Kathleen



From: Mierette Stocker [Mierette.Stocker@regeneron.com]

Sent: Wednesday, February 20, 2008 6:03 PM

FEB 25 2008

To: Davies, Kathleen

Subject: BLA 125249 Final Product Specifications

Attachments: 1.11.1 ARCALYST final product specs_final for submission.pdf; emfinfo.txt

Dear Kathleen,

Please find enclosed one document that consolidates all the final specification tables. This will be submitted to the eCTD in Module 1.11.1. The relevant specification tables within the eCTD will also be updated. I am hopeful that the submission will occur by the end of the week.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

(E)

20 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

From: Mierette Stocker
Sent: Friday, February 15, 2008 11:46 AM
To: _____
Subject: FW: BL 125249/Arcalyst - follow up to Product Specifications submission
Signed By: mierette.stocker@regeneron.com

Please archive to BLA 125249.
Subject: Product team reviewed alternative proposal for acceptance criteria and finds it acceptable.
Thanks
Mierette
O: 914-345-7590
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, February 15, 2008 10:27 AM
To: Mierette Stocker
Subject: RE: BL 125249/Arcalyst - follow up to Product Specifications submission

Hi Mierette,

The product team reviewed your alternative proposal and finds it acceptable for the criteria. Please submit to the BLA.

In addition, for ease of the reviewers, it would be helpful to get the tables as one unit to view (i.e., into Module 1.11.1.). In addition, the CTD sections should be updated to reflect the changes.

I also wanted to give you a heads up that we are in the process of finalizing our proposed label changes to the Arcalyst PI. I will email you (hopefully today) a word version that is a clean version and a pdf of our red-lined changes. Please keep an eye out for these documents.

Thanks,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Monday, February 11, 2008 9:00 AM
To: Davies, Kathleen
Subject: RE: BL 125249/Arcalyst - follow up to Product Specifications submission

Good morning Kathleen,

We would like discuss the acceptance criteria with the product reviewers today. We have prepared the enclosed document to form the basis for a discussion. Please forward to the appropriate reviewers. We sincerely would appreciate having a short discussion today, if possible. Please let me know when would be a good time.

Thanks

Mierette

2/15/2008

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, February 20, 2008 4:03 PM
To: 'Mierette Stocker'
Subject: RE: BL 125249/Arcalyst - Proposed Labeling

Km Davies

FEB 25 2008

Hi Mierette,

With regard to the immunogenicity section of the label, the clinical pharmacology reviewer offers the following clarification (see below). I wanted to provide it prior to the teleconference tomorrow so if you had further questions you could ask them at the teleconference.

Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Tuesday, February 19, 2008 10:47 AM
To: Davies, Kathleen
Subject: RE: BL 125249/Arcalyst - Proposed Labeling

Good morning Kathleen,

Thank you for the Division's comments to the PI and carton/container labels. We have reviewed and accepted most of the proposed changes to the PI. Enclosed, please find our

mark-up of the PI, which addresses comments from the Division and recommends additional changes for clarity. In addition, please find a file containing graphs of the 30, 50, and 70% responder rates over time, which was requested by the Division (see section 14 of the PI). Please forward these to the review team. We are available at any time if the Division wishes to discuss any of these proposed changes with us.

Please expect revised carton/container labels, which address all comments by the Division, by tomorrow.

Please let me know if you have any questions.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

Sent: Friday, February 15, 2008 6:14 PM

To: Mierette Stocker

Subject: BL 125249/Arcalyst - Proposed Labeling

Importance: High

Hi Mierette,

Please refer to BL 125249 for Arcalyst. Please find attached the Division's proposed wording for the PI and proposed changes to the carton and container labels. However, because there were such extensive changes to the label, a track changes version of the label does not provide any added benefit, but I included it so you could see where most of the changes occurred. Because there are extensive changes to the label, I suggest you conduct a side-by-side comparison of your version of the label and the Division's version of the label.

We request you provide us feedback on this label by Tuesday, February 20. At that time, we can determine a path forward as to what specific questions you have regarding our changes and any counter-proposals you would like to make.

Kind Regards,

Kathleen

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Wednesday, February 20, 2008 3:37 PM
To: Davies, Kathleen
Subject: BLA 125249 Revised container and carton labels
Attachments: 1112 ArcalystCarton-RV2-2.pdf; 1112 ArcalystLbl-RV2-2.pdf

FEB 25 2008

Km Davies

Dear Kathleen,

Please find enclosed revised carton and container labels, which we believe addresses FDA concerns. Please forward to the appropriate reviewers.

I would like to inquire about the availability of the license number that is required to appear on the vial and carton label. Since this is our first BLA, we are uncertain of when the license number is assigned. Can you clarify if the license number can be provided ahead of time (assuming that the final activities related to the BLA review continue to move ahead in an encouraging direction) so we can begin printing at risk? If we receive positive feedback on the vial and carton labels, we would like to begin the printing process, which will not be possible without the license number. Please understand that we are not trying to be presumptive regarding product approval. We are trying to build timelines for when commercial product can be made available to patients, if the product were to be approved. Any information you can provide will be helpful.

Please let me know if you have any questions.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

2/25/2008

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, February 19, 2008 5:01 PM
To: 'Mierette Stocker'
Subject: RE: BL 125249/Arcalyst - Proposed Labeling

FEB 25 2008

Importance: High**Attachments:** postmarketing commitments_FDA proposed.pdf; postmarketing commitments.doc*KM Davies*

Hi Mierette,

Thank-you for the labeling; I have passed it on to the review team. Please find attached the Division's proposed post-marketing items, grouped by discipline. Review these and provide completion dates.

We would like to speak with you on Thursday, February 21, between 3:00 - 4:00 PM to discuss the label and these commitments I've attached. We want to have some internal discussions first, so we will not call at 3:00, but I'm not sure exactly what time. Possibly 3:15-3:30. Let me know if this is acceptable for you and provide a call in number.

If you have any questions, let me know.

Thanks,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Tuesday, February 19, 2008 10:47 AM
To: Davies, Kathleen
Subject: RE: BL 125249/Arcalyst - Proposed Labeling

Good morning Kathleen,

Thank you for the Division's comments to the PI and carton/container labels. We have reviewed and accepted most of the proposed changes to the PI. Enclosed, please find our mark-up of the PI, which addresses comments from the Division and recommends additional changes for clarity. In addition, please find a file containing graphs of the 30, 50, and 70% responder rates over time, which was requested by the Division (see section 14 of the PI). Please forward these to the review team. We are available at any time if the Division wishes to discuss any of these proposed changes with us.

Please expect revised carton/container labels, which address all comments by the Division, by tomorrow.

Please let me know if you have any questions.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, February 15, 2008 6:14 PM
To: Mierette Stocker

Subject: BL 125249/Arcalyst - Proposed Labeling
Importance: High

Hi Mierette,

Please refer to BL 125249 for Arcalyst. Please find attached the Division's proposed wording for the PI and proposed changes to the carton and container labels. However, because there were such extensive changes to the label, a track changes version of the label does not provide any added benefit, but I included it so you could see where most of the changes occurred. Because there are extensive changes to the label, I suggest you conduct a side-by-side comparison of your version of the label and the Division's version of the label.

We request you provide us feedback on this label by Tuesday, February 20. At that time, we can determine a path forward as to what specific questions you have regarding our changes and any counter-proposals you would like to make.

Kind Regards,

Kathleen

F

3 Page(s) Withheld

✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Tuesday, February 19, 2008 10:47 AM
To: Davies, Kathleen
Subject: RE: BL 125249/Arcalyst - Proposed Labeling
Attachments: IL1T0505_response_line_305070_D42_byD7.pdf; PI_FDA proposed_clean_Regn 080219.doc; emfinfo.txt

K. Stocker
FEB 25 2008

Good morning Kathleen,

Thank you for the Division's comments to the PI and carton/container labels. We have reviewed and accepted most of the proposed changes to the PI. Enclosed, please find our mark-up of the PI, which addresses comments from the Division and recommends additional changes for clarity. In addition, please find a file containing graphs of the 30, 50, and 70% responder rates over time, which was requested by the Division (see section 14 of the PI). Please forward these to the review team. We are available at any time if the Division wishes to discuss any of these proposed changes with us.

Please expect revised carton/container labels, which address all comments by the Division, by tomorrow.

Please let me know if you have any questions.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, February 15, 2008 6:14 PM
To: Mierette Stocker
Subject: BL 125249/Arcalyst - Proposed Labeling
Importance: High

Hi Mierette,

Please refer to BL 125249 for Arcalyst. Please find attached the Division's proposed wording for the PI and proposed changes to the carton and container labels. However, because there were such extensive changes to the label, a track changes version of the label does not provide any added benefit, but I included it so you could see where most of the changes occurred. Because there are extensive changes to the label, I suggest you conduct a side-by-side comparison of your version of the label and the Division's version of the label.

We request you provide us feedback on this label by Tuesday, February 20. At that time, we can determine a path forward as to what specific questions you have regarding our changes and any counter-proposals you would like to make.

Kind Regards,

2/25/2008

Kathleen

BLANK
PAGE

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, February 15, 2008 6:14 PM
To: 'Mierette Stocker'
Subject: BL 125249/Arcalyst - Proposed Labeling
Importance: High
Attachments: Carton and Container Comments.pdf; PI_FDA proposed_red-lined..pdf; PI_FDA proposed_clean.doc

FEB 25 2008

KM Davies

Hi Mierette,

Please refer to BL 125249 for Arcalyst. Please find attached the Division's proposed wording for the PI and proposed changes to the carton and container labels. However, because there were such extensive changes to the label, a track changes version of the label does not provide any added benefit, but I included it so you could see where most of the changes occurred. Because there are extensive changes to the label, I suggest you conduct a side-by-side comparison of your version of the label and the Division's version of the label.

We request you provide us feedback on this label by Tuesday, February 20. At that time, we can determine a path forward as to what specific questions you have regarding our changes and any counter-proposals you would like to make.

Kind Regards,

Kathleen

G

1 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Davies, Kathleen~~FEB 25 2008~~*Kndavies*

From: Davies, Kathleen
Sent: Friday, February 15, 2008 10:27 AM
To: 'Mierette Stocker'
Subject: RE: BL 125249/Arcalyst - follow up to Product Specifications submission

FEB 25 2008

Kndavies

Hi Mierette,

The product team reviewed your alternative proposal and finds it acceptable for the — criteria. Please submit to the BLA.

In addition, for ease of the reviewers, it would be helpful to get the tables as one unit to view (i.e., into Module 1.11.1.). In addition, the CTD sections should be updated to reflect the changes.

I also wanted to give you a heads up that we are in the process of finalizing our proposed label changes to the Arcalyst PI. I will email you (hopefully today) a word version that is a clean version and a pdf of our red-lined changes. Please keep an eye out for these documents.

Thanks,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Monday, February 11, 2008 9:00 AM
To: Davies, Kathleen
Subject: RE: BL 125249/Arcalyst - follow up to Product Specifications submission

Good morning Kathleen,

We would like discuss the — acceptance criteria with the product reviewers today. We have prepared the enclosed document to form the basis for a discussion. Please forward to the appropriate reviewers. We sincerely would appreciate having a short discussion today, if possible. Please let me know when would be a good time.

Thanks

Mierette
O: 914-345-7590
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, February 08, 2008 9:01 AM
To: Mierette Stocker
Subject: BL 125249/Arcalyst - follow up to Product Specifications submission

Hi Mierette,

Please refer to BL 125249 for Arcalyst. The product review team had an opportunity to review your submission regarding the product specifications and has a few additional comments (see attached document).

2/25/2008

If you have any questions, please let me know.

Regards,

Kathleen

(H)

 1 Page(s) Withheld

 ✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

MEMORANDUM

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

DATE: February 13, 2008
TO: BLA File
FROM: Kathleen Davies, RPM
SUBJECT: **Pre-Approval Safety Conference**
BLA 125249, Arcalyst (rilonacept)

K. Davies Feb 27, 2008

The Pre-Approval Safety Conference for BL 125249 was intended to be apart of the wrap-up meeting held on October 18, 2007. Because the wrap-up meeting instead consisted of discussions regarding whether to have a major product amendment, a detailed discussion regarding post-marketing safety was not conducted.

OSE attendees of this wrap-up meeting included Suzane Berkman, Pharm.D., Senior Drug Risk Management Analyst, Mary Dempsey, Risk Management Coordinator, and Walter Fava R.Ph., Safety Evaluator. OSE recommended the implementation of a _____ and patient education materials (documented in the Review of proposed Risk Management Plan). The Division has requested the Sponsor implement _____ and will submit their patient education materials to DDMAC post-approval.

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Friday, February 08, 2008 5:58 PM
To: Davies, Kathleen
Subject: BLA 125249: Remaining response to Inquiries of Feb 4 TC
Attachments: BLA 125249_ _Cover Letter Attachment 3_Patient Training.pdf; emfinfo.txt

M. Stocker
FEB 25 2008

Dear Kathleen,

Please find enclosed the response to the second inquiry by Dr. Roca regarding patient training on the dose preparation and self-injection procedure. Please forward to Dr. Roca at your earliest convenience.

The _____ referenced in the attached document was included in this morning's response. The official eCTD submission of these responses by _____ will be on Tuesday or Wednesday of next week.

Please let me know if I can provide anything further regarding these responses.

Have a nice weekend.

Mierette
O: 914-345-7590
mierette.stocker@regeneron.com

From: Mierette Stocker
Sent: Friday, February 08, 2008 9:13 AM
To: Davies, Kathleen
Subject: BLA 125249: Partial response to Inquiries of Feb 4 TC

Dear Kathleen,

Please find enclosed the response to the first of Dr. Roca's inquiries regarding distribution of drug product and the ancillary supplies. Please forward to Dr. Roca at your earliest convenience. I hope to send the remainder of the response regarding patient training of the self-injection procedure by the end of today, but it may not be until Monday morning.

Please let me know if you have any questions.

Kind regards,

Mierette
O: 914-345-7590
mierette.stocker@regeneron.com

2/25/2008

Patient Training on Dose Preparation and Self-injection Procedures

In the IL1T-AI-0505 pivotal study in CAPS, subjects were instructed by clinic staff at the baseline visit in the use of aseptic technique to reconstitute study drug, withdraw the appropriate amount of drug from the vial into the injection syringe, and administer the subcutaneous (SC) injection. For pediatric subjects entering the study directly into the 24-week OLE, a parent/guardian (and the child, as appropriate) was taught dose preparation and injection technique. In addition, all subjects received written instructions on dose preparation and subcutaneous injection technique (patient training information is in Appendix 11.1.3 of IL1T-AI-0505 Part AB CSR). Sufficient time was to be allowed for practice.

In response to the request by FDA to provide an assessment of the effectiveness of the self-injection training provided, the 21 active study sites were contacted by phone to specifically query study staff regarding whether subjects understood the provided training materials. Responses were received from all 21 sites. Two responses indicated difficulty by subjects in understanding the instructions provided:

- Despite multiple training sessions with the subject and the subject's parents, a 20 year old female entered directly into the open label extension of the pivotal trial in 2007 has administered injection volumes varying between 1.8 and 2.4 mL, rather than the specified 2.0 mL.
- An 80 year old female subject entered directly into the open label extension of the pivotal trial in 2007 initially had trouble understanding the training materials and required longer training sessions for full understanding of how to reconstitute the vial and self-inject.

To further assess the effectiveness of the self-injection information and training that the subjects received, the study database was examined. In the database¹, 2399 injections of study drug were administered to subjects in the study. The data within the drug administration electronic case report form pages were queried for:

¹ dated March 30, 2007 that was provided in the BLA, which includes the experience of 59 CAPS subjects in study IL1T-AI-0505 up to and including the dose prior to the 48-week (24-week OLE) visit.

- 1) recorded injection volumes other than 2.0 mL, which would be incorrect except for pediatric subjects whose weight-adjusted dose volume might be specified to be less than 2.0 mL, and
- 2) reasons for missed doses, which were to be included in the comment field for any missed dose.

Overall, 9 (0.4%) administered dose volumes were not as specified, with incorrect dose volumes administered in 3 subjects. In 2 subjects (59 year old male; 26 year old female), 7 incorrect dose volumes between 2.1 and 2.3 mL were self-injected early in the study, which was corrected by additional subject education by site personnel. In one subject, 2 incorrect dose volumes, 2.3 mL and 3.4 mL, were injected by the subject's caregiver [Note: because the volume of drug in a correctly reconstituted vial of rilonacept is considerably less than 3.4 mL and because the syringes provided for injection do not allow for measured injections above 3.0 mL, the 3.4 mL record in the database likely represents a recording error by the subject. The 3.4 mL volume was identified for query but resolved "as is" based on monitoring of the injection volume recorded by the subject]. This subject was discontinued from the study for non-compliance for additional, unrelated reasons.

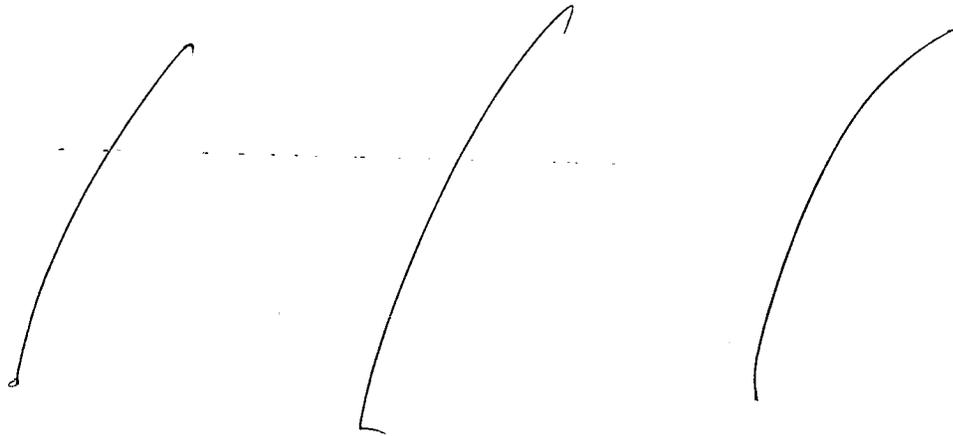
Twenty seven (27) records were identified among 12 patients that indicated a missed dose. None of the reasons provided for the missed dose indicated that any were missed due to a reason potentially related to inadequate understanding of dose preparation or injection technique.

Injection site reactions, which were the most frequently reported adverse event in the IL1T-AI-0505 study in CAPS, as well as in other studies of rilonacept, have the potential to be related to poor injection technique. However, the greater frequency of injection site reactions reported in subjects administering rilonacept relative to placebo, argues strongly against poor dose preparation or injection technique as an important cause of injection site reactions. Importantly, query of the study database for infection at the injection site (MedDRA preferred term "injection site infection"), an adverse event likely related to poor technique, did not reveal any such reported infections.

In summary, training and materials provided to subjects for dose preparation and subcutaneous injection technique during the course of the pivotal study in CAPS appeared to be adequate for patients to comply with the study conduct. Administration of incorrect dose volumes by subjects was rare and generally correctable, and no administrations were identified as having been missed due to reasons potentially related to inadequate understanding of dose preparation or injection

technique. The pattern of reported injection site reactions appeared to be attributable to characteristics of the study drug rather than improper dose preparation or injection technique. In conclusion, the assessments indicate that the materials and training provided to subjects in the CAPS clinical trial were effective in teaching safe, proper technique for drug reconstitution, dose preparation, and drug injection.

For commercial drug, 



Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Friday, February 08, 2008 9:13 AM
To: Davies, Kathleen
Subject: BLA 125249: Partial response to Inquiries of Feb 4 TC
Attachments: BLA 125249_Cover Letter Attachment 2_Distribution of ARCALYST and ancillary supplies.pdf; emfinfo.txt

FEB 25 2008
Km Davies

Dear Kathleen,

Please find enclosed the response to the first of Dr. Roca's inquiries regarding distribution of drug product and the ancillary supplies. Please forward to Dr. Roca at your earliest convenience. I hope to send the remainder of the response regarding patient training of the self-injection procedure by the end of today, but it may not be until Monday morning.

Please let me know if you have any questions.

Kind regards,

Mierette

O: 914-345-7590

mierette.stocker@regeneron.com

2/25/2008



20 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Monday, February 04, 2008 9:49 AM
To: 'Mierette Stocker'
Subject: teleconference today, Monday Feb 4
Importance: High

FEB 25 2008

Km Davies

Hi Mierette,

I just left you a voice message. I apologize for the short notice, but Dr. Roca wanted to speak with Regeneron today to ask some questions about how the product is currently supplied, as described in the label. He believes that it is likely a question that clinical/regulatory could answer.

The best time for him to speak with you is 1:30 pm (EST); please let me know if this would be acceptable at your earliest convenience.

Thanks so much,

Kathleen

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Thursday, January 17, 2008 6:59 AM
To: Davies, Kathleen
Subject: BLA 125249 Commitments from Jan 16 TC
Attachments: BLA 125249 FDA mtg 16 Jan 2008_commitments.pdf; emfinfo.txt

Kathleen Davies
JAN 18 2008

Dear Kathleen,

Enclosed please find a summary of Regeneron's commitments from yesterday's TC. Please let me know as soon as possible if the reviewers believe that any of these are inaccurate. I will try to regularly provide status updates on the availability of our responses with the intention that we will provide all information to FDA by early next week.

Thanks and kind regards,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

4 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Wednesday, January 16, 2008 12:49 PM
To: Davies, Kathleen
Cc: William Roberts
Subject: RE: BLA 125249/II-1 Trap - Items for discussion today
Attachments: emfinfo.txt

JAN 18 2008
William Roberts

Thank you for the information Kathleen. We accept FDA's comments to Items 1, 2, 6, 11 and 12. We would like to discuss the remainder of the comments with the reviewers during our TC this afternoon.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Wednesday, January 16, 2008 9:10 AM
To: Mierette Stocker
Cc: William Roberts
Subject: BLA 125249/II-1 Trap - Items for discussion today
Importance: High

Good morning Mierette,

Please refer to your BLA 125249 for IL-1 Trap. Please find the items for the teleconference today at 1:00 PM attached.

This teleconference today is because we must have these items finalized today and we need them sent to the BLA. IF any of these items are simple "yes", please let me know prior to the teleconference if possible, so that we can facilitate discussion to only discuss items that need discussion.

If you have any questions, please let me know.

Kind Regards,

Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, January 16, 2008 9:10 AM
To: 'Mierette Stocker'
Cc: ; 'william.roberts@regeneron.com'
Subject: BLA 125249/II-1 Trap - Items for discussion today
Importance: High
Attachments: 1-16-08 Specification teleconference.pdf



FEB 25 2008

Good morning Mierette,

Please refer to your BLA 125249 for IL-1 Trap. Please find the items for the teleconference today at 1:00 PM attached.

This teleconference today is because we must have these items finalized today and we need them sent to the BLA. IF any of these items are simple "yes", please let me know prior to the teleconference if possible, so that we can facilitate discussion to only discuss items that need discussion.

If you have any questions, please let me know.

Kind Regards,

Kathleen

Ⓚ

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Silver Spring, MD 20903
Tel. 301-796-1672

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125149/0

Name of Drug: Riloncept

Sponsor: Regeneron Pharmaceuticals, Inc.

Material Reviewed: Arcalyst™ (riloncept) Carton and Container Labels

OBP Receipt Date: February 7, 2008

Background:

Regeneron Pharmaceuticals, Inc. has submitted a Biologic License Application (BLA) for Arcalyst (riloncept) a lyophilized product containing 220 mg of Interleukin-1 (IL-1) Trap in a sterile, single-use vial. Arcalyst (riloncept) is being developed for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

Labels Reviewed:

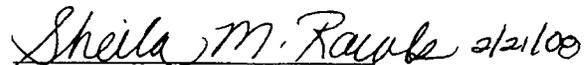
Arcalyst™ (riloncept) Container Label
Arcalyst™ (riloncept) Carton Label

Review

The carton and container labels for Arcalyst™ (riloncept) were reviewed and conformed to the most of the regulations found under the following Code of Federal Regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.1 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. Please see the comments in the conclusions section.

Conclusions:

- The lot number and expiration date are not expressed on the container label according to 21 CFR 610.60 (3) and (4). These items should be located on the label.
- The lot number and expiration date are not expressed on the carton label according to 21 CFR 610.61 (c) and (d). These items should be located on the label.
- It is difficult to read the strength. The  color indicating the strength should be a darker and different color.
- More spacing between the proper name and the strength is recommended on the container label.
- Please lower the "Rx Only" on the container label.



Sheila M. Rawls
Regulatory Project Manager
CDER/OPS/OBP/IOD

Comment/Concurrence: I concur.



Ruth Cordoba-Rodriguez, Ph.D.
Product Reviewer
CDER/OPS/OBP/DMA

②

 7 Page(s) Withheld

 Trade Secret / Confidential

 / Draft Labeling

 Deliberative Process

Delasko, Jeanne

Jeanne Delasko

From: Delasko, Jeanne
Sent: Tuesday, February 12, 2008 11:18 AM
To: Davies, Kathleen
Cc: Burke, Laurie B; Thompson, Elizabeth; Araujo, Richardae; Feibus, Karen; Siegel, Jeffrey
Subject: Comments: BL 125249 (Arcalyst)
Attachments: JMDelasko08Araujo.02.12.08.doc

FEB 13 2008

Hi Kathleen,

Here are the SEALD and MHT comments. Let me know if you have questions.

Jeanne

15 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Davies, Kathleen

From: Chi, Bo
Sent: Tuesday, February 05, 2008 9:58 AM
To: Davies, Kathleen
Subject: FW: Compliance check (Please provide it on January 22nd.)

Kathleen, this is the EER for the labeling and packaging facility _____ for BLA 125249/0.

Bo

FEB 5 2008

Km Davies

From: Ferguson, Shirnette D
Sent: Tuesday, January 22, 2008 9:06 AM
To: Chi, Bo; CDER-TB-EER
Subject: RE: Compliance check (Please provide it on January 22nd.)

The Manufacturing Assessment and Pre-approval Compliance Branch has completed its review and evaluation of the compliance check below. There are no ongoing or pending compliance actions that would prevent approval of STN 125249/0 at this time. _____ was last inspected on 11/19-11/21/2007 and found acceptable for classified NAI. That inspection was

Shirnette

From: Chi, Bo
Sent: Friday, January 18, 2008 4:39 PM
To: CDER-TB-EER
Subject: Compliance check (Please provide it on January 22nd.)

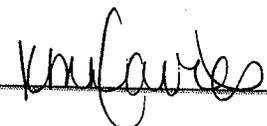
Hi, could you please provide establishment evaluation of _____ in support of approving BLA STN 125249/0? The memo for this BLA is due next Tuesday, January 22nd, could you provide the compliance check on Tuesday morning? Thanks. Sorry for the short notice.

Proposed Labeling and Packaging of DP

✓

Thanks.

Bo

Davies, Kathleen**From:** Mierette Stocker [Mierette.Stocker@regeneron.com]**Sent:** Thursday, January 10, 2008 10:01 PM**To:** Davies, Kathleen

JAN 1 8 2008

Subject: RE: BL 125249 - Follow up**Attachments:** RILONACEPT MEDWATCH REPORT 0711-352.pdf; emfinfo.txt

Dear Kathleen,

Follow-up information was provided to Regeneron by the clinical site on 08 Jan 2008 after I sent you the note below. The site learned that the Coroner did perform an autopsy. A death certificate was provided, which listed the cause of death as coronary atherosclerosis. The Study Coordinator has attempted to obtain the autopsy report from the Office of Vital Records in _____ but this will need to be requested by the subject's wife. The subject's wife agreed to request that report and to send this report to the study site once it is received. The Investigator rated the severity of the event (coronary atherosclerosis) as severe and the causality as not related to rilonacept. A follow-up Medwatch 3500A report for this subject is enclosed and will be submitted to the rilonacept INDs as a 15-day report. Additionally, the initial and follow-up Medwatch reports will be submitted to the BLA. These submissions will occur towards the end of next week because I will be traveling for business through Jan 15th as I communicated to you in an earlier e-mail today.

Please forward this information to the appropriate medical reviewers.

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com**From:** Mierette Stocker**Sent:** Tuesday, January 08, 2008 12:16 PM**To:** Davies, Kathleen**Subject:** RE: BL 125249 - Follow up

Dear Kathleen,

We submitted a follow-up report (via FedEx and e-mail) on Dec 20, 2007 to the rilonacept INDs, which explained that we have been unable to obtain significant new information since we first reported the subject's death, despite many attempts by Regeneron and by the investigational site. I have enclosed this report again for your convenience. Specific details regarding our contact with the clinical site and the site's contact with the family are as follows:

- Between 01-Nov-2007 through 03-Jan-2008, the Regeneron Medical Safety department has made nine telephone calls and sent one facsimile to the site in an effort to obtain additional information.
- Between 05-Nov-2007 and 18-Dec-2007, the Study Coordinator reported and has documented nine telephone calls to the subject's family. Four of those nine calls resulted in the Study Coordinator speaking with the subject's mother who reported the date of the subject's death and some brief details. According to the Study Coordinator, the subject's mother has continually stated that no death certificate has been received and that the subject's wife is unavailable.
- According to the Principal Investigator, the site has been in contact with the Coroner's Office located in _____ which indicated that even as the subject's treating physician, they will not release any information to her and that she is not eligible to receive the death certificate. The Coroner's Office will provide their written, formal evaluation to the family when it is completed. The family has indicated

1/18/2008

that they will forward any new information to the Principal Investigator once it becomes available.

- On 18-Dec-2007, Steven Weinstein, MD, PhD (Regeneron's Vice President, Inflammation) visited the site, reviewed the subject's medical records, and met with the Principal Investigator and Study Coordinator. This visit confirmed that the site has been unable to obtain additional information. The Principal Investigator has committed to continue attempts to learn if an autopsy was performed and to obtain any new information from the family.

To date, Regeneron has been unable to confirm that an autopsy was performed or to gain any significant new information. If the site is unable to obtain any new information, then we will explore direct contact with the Coroner's office if we determine that such contact is legally permissible.

I will provide the above information in a written communication to the BLA next week.

Please let me know if the clinical team has any further questions

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

Sent: Sunday, January 06, 2008 9:25 PM

To: Mierette Stocker

Subject: BL 125249 - Follow up

Hi Mierette,

Please refer to BL 125249 for IL-1 Trap. We spoke a few weeks ago regarding the safety report notifying the agency of the person enrolled in your study who died. The clinical team requests you again follow up with the site, specifically:

Mfr. Rept No. 0711-352 re patient ID 017-2013 reported sudden death of this patient on _____ In this communication an autopsy report was expected to be concluded within 1-2 months. Please determine if one was done, and if so contact the study site investigator or coroner to obtain the results.

Let me know if you have any questions.

Kathleen

For use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting
Page 1 of 3

MEDWATCH

FD-3500A (10/05)

Mfr Report # 0711-352
UF/Importer Report #
FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier: 017-2013
2. Age at Time of Event: 37 Y
3. Sex: Female Male
4. Weight: 108.9 kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
 Death (mm/dd/yyyy) Disability or Permanent Damage
 Life-threatening Congenital Anomaly/Birth Defect
 Hospitalization - initial or prolonged Other serious (Important Medical Events)
 Required intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy):
4. Date of This Report (mm/dd/yyyy): 01/10/2008

5. Describe Event or Problem
 IL1T-AI-0505: A Multicenter, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Efficacy of IL-1 Trap in Subjects with CIAS1 Associated Periodic Syndromes (CAPS) Using Both Parallel Group and Randomized Withdrawal Designs.
 Study Coordinator reported to Regeneron on 01-Nov-2007 that this 37 year old Caucasian male subject, participating in the Riloncept study, IL1T-AI-0505 for Cryopyrin Associated Periodic Syndromes (CAPS), died suddenly at home in . The subject had a history Familial Cold Autoinflammatory Syndrome (FCAS) diagnosed at birth to 6 months, asthma since 1972, seasonal allergies and hypertension at baseline and during the study with blood pressures on (Screening) 144/82, (Baseline Day 0) 152/93, (Open Label Week 6) 139/79, (Open Label Week 12) 141/81; and (Open Label Week 24) 146/100. The subject had no history of alcohol abuse and stopped smoking more than 10 years ago. The subject's concomitant medications included Astelin taken nasally as needed for allergies since
 CONTINUED

6. Relevant Tests/Laboratory Data, Including Dates
 Screening ECG - Normal, QTc interval 402 msec.
 Open Label Week 6 ECG - Normal, QTc interval 399 msec.
 Calculated baseline BMI: 38.2 kg/m2.
 Blood Pressures:
 (Screening) - 144/93
 (Baseline Day 0) - 152/93
 (Open Label Week 12) - 141/81
 (Open Label Week 24) - 146/100
 CONTINUED

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
 Risk Factors : Allergy
 Familial Cold Autoinflammatory Syndrome (FCAS) diagnosed birth to 6 months
 Seasonal Allergies
 Asthma since 1972
 Stopped smoking more than 10 years ago
 hypertension at baseline

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)
 #1 RILONACEPT (Injection) (riloncept)
 #2

2. Dose, Frequency & Route Used
 #1 160 mg, QWK, Subcutaneous
 #2
 3. Therapy Dates (If unknown, give duration from/to (or best estimate))
 #1 03/29/2007 - Unknown
 #2

4. Diagnosis for Use (Indication)
 #1 Familial cold autoinflammatory syndrome
 #2
 5. Event Abated After Use Stopped or Dose Reduced?
 #1 Yes No Doesn't Apply
 #2 Yes No Doesn't Apply

6. Lot #
 #1
 #2
 7. Exp. Date
 #1
 #2

8. Event Reappeared After Reintroduction?
 #1 Yes No Doesn't Apply
 #2 Yes No Doesn't Apply

9. NDC # or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
 1) Astelin 03/29/2007 - 10/29/2007

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)
 REGENERON PHARMACEUTICALS, INC.
 REGULATORY DEVELOPMENT
 777 OLD SAW MILL RIVER ROAD
 TARRYTOWN, NY 10591-6707
 USA
 (Informing Unit)

2. Phone Number: 914-345-7400

3. Report Source (Check all that apply)
 Foreign
 Study
 Literature
 Consumer
 Health Professional
 User Facility
 Company Representative
 Distributor
 Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 01/08/2008
 5. (A)NDA #
 IND # 11781
 STN #
 PMA/510(k) #
 Combination Product Yes
 Pre-1938 Yes
 OTC Product Yes

6. If IND, Give Protocol #
 IL1T-AI-0505

7. Type of Report (Check all that apply)
 5-day 30-day
 7-day Periodic
 10-day Initial
 15-day Follow-up # 1

8. Adverse Event Term(s)
 1) Arteriosclerosis
 CONTINUED

9. Manufacturer Report Number: 0711-352

E. INITIAL REPORTER

1. Name and Address
 Phone #

2. Health Professional? Yes No
 3. Occupation: Study
 4. Initial Reporter Also Sent Report to FDA Yes No Unk.
 CONTINUED

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

29-Mar-2007. The subject enrolled directly into the open label portion of the study and received his first dose of riloncept 160 mg sc on 29-Mar-2007. The subject received weekly subcutaneous doses of riloncept 160 mg. The date of the last dose of study drug prior to the subject's death is unknown. Most laboratory values at baseline and throughout the study period were within the normal range. Calculated baseline BMI was 38.2 kg/m². Increased laboratory values at baseline were noted for CRP 47.6 (0-8.4 mg/L), Platelets 387 (125-375 k/mm³), Calc. VLDL cholesterol 55 (9-40 mg/dl) and triglycerides 275 (45-200 mg/dl). By study week 6, triglyceride values increased 3-fold to 865 mg/dl but the subject remained asymptomatic. Triglycerides decreased to 566 mg/dl by study week 24. Adverse Events reported by the subject during the study included: injection site redness on 12-Apr, 19-Apr, and 26-Apr-2007 considered mild in severity and resolved, and hypertriglycerides on 11-May-2007, considered mild in severity, ongoing and not related to study drug by the Investigator. Electrocardiograms (ECG) at screening [redacted] and at week 6 [redacted] were normal with QTc intervals of 402 and 399 msec., respectively. The last telephone contact with the subject occurred on 25-Oct-2007 at which time no adverse events or concomitant medication changes were reported. According to the Study Coordinator, autopsy results will not be available for 1-2 months. Additional information received from the Study Coordinator on 07-Nov-2007, indicates that the subject died on [redacted]. According to the Investigator (01-Nov-2007), the event (sudden death) was severe and the causality cannot be assessed until further information is obtained.

Follow-up information (including the death certificate) reported to Regeneron by the Study Coordinator on 08-Jan-2008 indicated that the subject died at home (sudden death) and was never hospitalized. As per the Study Coordinator, the Coroner performed an autopsy and found no evidence of criminal activity. The Death Certificate provided the cause of death as coronary atherosclerosis. Obesity was listed on the serious adverse event form as a contributing factor. The Study Coordinator attempted to obtain the autopsy report from the Office of Vital Records in [redacted] but this will need to be requested by the subject's wife. The subject's wife agreed to send this report to the study site once it is received. The following laboratory results Cholesterol, HDL Cholesterol, LDL Cholesterol and non-HDL Cholesterol, from [redacted], are provided. According to the Investigator, (08-Jan-2007), the severity of the event (coronary atherosclerosis) was severe and was not related to riloncept. The potential alternative explanation was due to other known or suspected cause.

Coronary atherosclerosis is unexpected in the current Investigator's Brochure for riloncept.

Company Comment:

08-Nov-2007: Subject 017-2013 was a 37 year old obese male with a history of asthma and seasonal allergies being treated with Astelin (prn), as well as untreated hypertension noted at baseline and during the study. The subject was participating in the open label phase of the riloncept trial since 29-Mar-2007. On [redacted] he was reported to have died from unspecified causes. Based on the limited available information and currently known safety profile of riloncept, the sponsor assesses the case as not related to the study drug. Additional information is being sought.

15-Nov-2007: This case was not submitted as a 15-Day IND Safety Report. No additional information was received after several attempts to obtain follow-up information were made.

10-Jan-2008: Based on the pre-existing condition (i.e., obesity, hypertriglyceridemia, and untreated hypertension noted at baseline), the known safety profile of riloncept and the autopsy report indicating the patient had coronary atherosclerosis, the Sponsor continues to assess the case as not related to study drug.

B.6 Relevant Tests/Laboratory Data, Including Dates (Cont...)

10-May-2007: (Open Label Week 6) - 139/79

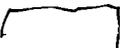
18-Dec-2007: Death certificate: Cause of death: Coronary atherosclerosis

C Continuation Sheet for FDA-3500A Form

Mfr. Report # : 0711-352

Date of This Report : 01/10/2008

Lab Result :

Test name	Test date	Test result	Normal value
Calc. VLDL Cholesterol		55 mg/dL	9 - 40
Cholesterol		61 mg/dL	9 - 40
		198 mg/dL	125 - 200
		190 mg/dL	125 - 200
		243 mg/dL	125 - 200
		256 mg/dL	125 - 200
CRP		255 mg/dL	125 - 200
		47.600 mg/L	0.000 - 8.400
		2.200 mg/L	0.000 - 8.400
		1.900 mg/L	0.000 - 8.400
Direct HDL		1.400 mg/L	0.000 - 8.400
		38 mg/dL	35 - 60
		32 mg/dL	35 - 60
		30 mg/dL	35 - 60
		30 mg/dL	35 - 60
LDL Chol		32 mg/dL	35 - 60
		105 mg/dL	50 - 160
		97 mg/dL	50 - 160
Non-HDL Cholesterol		160 mg/dL	65 - 165
		158 mg/dL	65 - 165
		213 mg/dL	65 - 165
		226 mg/dL	65 - 165
		223 mg/dL	65 - 165
Platelet		387 K/mm3	125 - 375
		342 K/mm3	125 - 375
		388 K/mm3	125 - 375
		350 K/mm3	125 - 375
		350 K/mm3	125 - 375
		350 K/mm3	125 - 375
Triglycerides		275 mg/dL	45 - 200
		305 mg/dL	45 - 200
		865 mg/dL	45 - 200
		668 mg/dL	45 - 200
		566 mg/dL	45 - 200
		566 mg/dL	45 - 200

C.10 Concomitant Medical Products and Therapy Dates

Seq No. : 1
 Concomitant Medical Product : Astelin
 Dose, Frequency & Route Used : 1) , PRN, Nasal
 Diagnosis for Use (Indication) : 1) Seasonal allergy

E. INITIAL REPORTER (Cont...)

Occupation: Study Coordinator

E. INITIAL REPORTER

Other Reporters

2

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

1) Arteriosclerosis coronary artery

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Tuesday, January 08, 2008 12:16 PM
To: Davies, Kathleen
Subject: RE: BL 125249 - Follow up
Attachments: BB-IND 11781-142_ *SAE0505.pdf*;
emfinfo.txt

Dear Kathleen,

We submitted a follow-up report (via FedEx and e-mail) on Dec 20, 2007 to the riloncept INDs, which explained that we have been unable to obtain significant new information since we first reported the subject's death, despite many attempts by Regeneron and by the investigational site. I have enclosed this report again for your convenience. Specific details regarding our contact with the clinical site and the site's contact with the family are as follows:

- Between 01-Nov-2007 through 03-Jan-2008, the Regeneron Medical Safety department has made nine telephone calls and sent one facsimile to the site in an effort to obtain additional information.
- Between 05-Nov-2007 and 18-Dec-2007, the Study Coordinator reported and has documented nine telephone calls to the subject's family. Four of those nine calls resulted in the Study Coordinator speaking with the subject's mother who reported the date of the subject's death and some brief details. According to the Study Coordinator, the subject's mother has continually stated that no death certificate has been received and that the subject's wife is unavailable.
- According to the Principal Investigator, the site has been in contact with the Coroner's Office located in _____ which indicated that even as the subject's treating physician, they will not release any information to her and that she is not eligible to receive the death certificate. The Coroner's Office will provide their written, formal evaluation to the family when it is completed. The family has indicated that they will forward any new information to the Principal Investigator once it becomes available.
- On 18-Dec-2007, Steven Weinstein, MD, PhD (Regeneron's Vice President, Inflammation) visited the site, reviewed the subject's medical records, and met with the Principal Investigator and Study Coordinator. This visit confirmed that the site has been unable to obtain additional information. The Principal Investigator has committed to continue attempts to learn if an autopsy was performed and to obtain any new information from the family.

To date, Regeneron has been unable to confirm that an autopsy was performed or to gain any significant new information. If the site is unable to obtain any new information, then we will explore direct contact with the Coroner's office if we determine that such contact is legally permissible.

I will provide the above information in a written communication to the BLA next week.

Please let me know if the clinical team has any further questions

Kind regards,

Mierette
O: 914-345-7590
M: 914-548-4390
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Sunday, January 06, 2008 9:25 PM
To: Mierette Stocker

1/18/2008

Subject: BL 125249 - Follow up

Hi Mierette,

Please refer to BL 125249 for IL-1 Trap. We spoke a few weeks ago regarding the safety report notifying the agency of the person enrolled in your study who died. The clinical team requests you again follow up with the site, specifically:

Mfr. Rept No. 0711-352 re patient ID 017-2013 reported sudden death of this patient on . In this communication an autopsy report was expected to be concluded within 1-2 months. Please determine if one was done, and if so contact the study site investigator or coroner to obtain the results.

Let me know if you have any questions.

Kathleen

REGENERON

**REGENERON PHARMACEUTICALS, INC.
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591-6707
TELEPHONE: 914-345-7590
FACSIMILE: 914-345-7688
E-MAIL: miette.stocker@regeneron.com**

**Mierette R. Stocker
Director, Regulatory Affairs**

December 20, 2007

Ms. Kathleen Davies,
Ms. Margaret Pease-Fye
Ms. Florence O. Moore
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologics Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Information Amendment: Clinical

BB-IND 11781-142

Dear Ms. Davies, Pease-Fye and Moore:

Please refer to the 08 Nov 2007 communication¹ of an initial report of a serious adverse event (sudden death) in a subject participating in the long-term open-label extension phase of study IL1T-AI-0505 entitled "A Multi-center, Double-Blind, Placebo-Controlled, Study of the Safety, Tolerability, and Efficacy of IL-1 Trap in Subjects with *CIAS1*-Associated Periodic Syndromes (CAPS) Using Both Parallel Group and Randomized Withdrawal Designs".

Additional follow-up information has been sought regarding the circumstances of the subject's death. Regeneron has frequently and regularly contacted the investigational site to inquire about the availability of new information. The investigational site has made numerous attempts to contact the subject's family and to contact the coroner in order to determine if an autopsy was performed. As of this time, there is no, new significant information to provide. Regeneron's Medical Monitor recently visited the investigational site, reviewed the subject's medical records and confirmed with the principal Investigator that the site has been unable to learn any new details. The Principal Investigator has committed to continue attempts to learn if an autopsy was performed and to obtain

¹ BB-IND 11781-139,

Regeneron Pharmaceuticals, Inc.

BB-IND 11781-142,

December 20, 2007

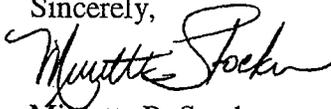
Page 2 of 2

new information from the family. Regeneron will continue to follow-up with the investigational site and will provide any significant new information to FDA as soon as it is available.

We consider the information contained in this submission to be confidential and ask that the FDA not disclose its contents to any other parties without prior written consent from Regeneron Pharmaceuticals, Inc.

If you have further questions, please do not hesitate to call me at (914) 345-7590. In the event that I cannot be reached and the Agency has a concern that requires immediate attention, you may contact Dr. William Roberts at (914) 345-7940.

Sincerely,



Mierette R. Stocker

Director, Regulatory Affairs

Electronic mail: Ms. Kathleen Davies, December 20, 2007