CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022150Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22150 SUPPL # 000 HFD # 570

Trade Name Firazyr

Generic Name icatibant

Applicant Name Shire Orphan Therapies, Inc (formerly Jerini US Inc.)

Approval Date, If Known August 25, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

The sponsor did not ask for exclusivity. However, this is an NME and an orphan drug.

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

similar investigation was relied on:

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

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

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

Investigation #1 ! !

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !

IND # YES ☐ ! NO ☐
! Explain:

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

Investigation #1 ! !

YES ☐ ! NO ☐

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Eunice Chung-Davies, Pharm.D.
Title: Regulatory Project Manager, Division of Pulmonary, Allergy and Rheumatology Products
Date: July 28, 2011

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Director, Division of Pulmonary, Allergy and Rheumatology Products

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

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

/s/

EUNICE H CHUNG-DAVIES
08/25/2011

BADRUL A CHOWDHURY
08/25/2011

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22150 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Pulmonary, Allergy, and Rheumatology Products PDUFA Goal Date: August 25, 2011 Stamp Date: 2/25/2011

Proprietary Name: Firazyr

Established/Generic Name: icatibant

Dosage Form: Injection

Applicant/Sponsor: Shire Orphan Therapies, Inc (formerly Jerini)

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of hereditary angioedema (HAE) in adults 18 years of age and older

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

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

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Drafted by: EChung-Davies/29JUL2011
Initialed by: SBarnes/10Aug2011
Sent to: GGreeley/11Aug2011

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

/s/

EUNICE H CHUNG-DAVIES
08/12/2011

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-150 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: October 26, 2007 **PDUFA Goal Date:** April 26, 2007

HFD: 570 **Trade and generic names/dosage form:** Firazyr (icatibant) 30 mg (b) (4)

Applicant: Jerini US **Therapeutic Class:** bradykinin type 2 receptor antagonist

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 question.**

☐ **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): one

Indication #1: treatment of acute attacks of hereditary angioedema (HAE)

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. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

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 DFS.

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 DFS.

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 DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

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 DFS.

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 DFS.

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Sandra Barnes
1/16/2008 11:09:49 AM

1.3.3 DEBARMENT CERTIFICATION

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §335a(k), as amended by the Generic Drug Enforcement Act of 1992, we, Jerini US Inc., state the following with respect to this new drug application:

Jerini US Inc., hereby certifies that it did not and will not use in any capacity the services of a person debarred under section 306 of the Federal, Food, Drug, and Cosmetic Act in connection with this application.

Signature: Date: 19/10/07

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22-150 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Firazyr Established/Proper Name: icatibant Dosage Form: injection		Applicant: Shire Orphan Therapies (formerly Jerini U.S.) Agent for Applicant (if applicable):
RPM: Eunice Chung-Davies		Division: Division of Pulmonary, Allergy, and Rheumatology Products

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

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

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

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

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

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

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

☐ No changes ☐ Updated Date of check:

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

❖ Actions	
• Proposed action • User Fee Goal Date is August 25, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None NA: 4/23/2008

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

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

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

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

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

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

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

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

Comments: Resubmission

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

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

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

Version: 4/21/11

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (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))).	☐ Yes ☐ No
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (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))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	8/25/2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval: 8/25/2011; NA: 4/23/2008
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	8/17/2011
• Original applicant-proposed labeling	2/25/2011; 10/27/2007
• Example of class labeling, if applicable	N/A

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

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	8/17/2011
• Original applicant-proposed labeling	7/12/2011
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	8/17/2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	6/9/2011 6/9/2011; 5/9/2007
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 4/22/2011;12/21/2007 ☒ DMEPA 6/21/2011;3/10/2008 ☒ DRISK 8/1/2011;7/14/2011 ☒ DDMAC 7/18/2011; 7/15/2011; 11/20/2007 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	1/16/2008 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Drug Designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

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

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	8/15/2011;8/9/2011; 8/2/2011; 8/1/2011; 7/29/2011;7/25/2011; 7/18/2011; 7/15/2011; 7/8/2011; 6/12/2011; 5/24/2011; 5/12/2011; 5/6/2011; 5/2/2011; 4/18/2011; 3/5/2011; 4/22/2008; 2/26/2008; 2/14/2008; 1/31/2008; 1/8/2008; 12/20/2007; 12/12/2007; 11/6/2007
❖ Internal memoranda, telecons, etc.	8/17/2011; 8/5/2011; 7/27/2011; 7/20/2011; 7/12/2011; 7/6/2011; 1/31/2008; 1/23/2008; 8/18/2005
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg 6/17/2008 (Canceled)
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1/24/2007;3/1/2005
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 3/5/2008; 7/1/2004
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	3/5/2008 (90 day conference); 2/6/2004 (PIND meeting)
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	June 23, 2011
• 48-hour alert or minutes, if available *(do not include transcript)*	June 23, 2011
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 8/25/2011; 4/23/2008
Division Director Summary Review *(indicate date for each review)*	☐ None 8/24/2011; 4/23/2008
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/8/2011; 3/20/2008
PMR/PMC Development Templates *(indicate total number)*	☐ None 8/19/2011(3)
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A (see CDTL memo)
• Clinical review(s) *(indicate date for each review)*	8/23/2011; 7/25/2011; 4/14/2011; 2/29/2008; 12/19/2007
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	In primary clinical review, dated 7/25/2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 5/26/2011 (QTIRT)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable

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

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 3/31/2008
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 6/29/2011
Statistical Review(s) *(indicate date for each review)*	☐ None 6/29/2011; 3/21/2008
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/14/2011; 3/21/2008
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 8/19/2011
• Supervisory Review(s) *(indicate date for each review)*	☐ None 8/1/2011
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/23/2011; 4/3/2008; 3/18/2008; 12/20/2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None 11/3/2010; 6/11/2008 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 8/24/2011; 8/5/2011; 3/17/2008
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 8/1/2011; 3/25/2008
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7/27/2011; 3/13/2008; 12/21/2007
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/3/2011; 3/11/2008
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 8/9/2011;7/27/2011 (CDRH); 7/23/2011 (PT); 3/14/2008 (PT)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	In CMC review, dated 3/13/2008
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 8/25/2011 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

EUNICE H CHUNG-DAVIES
08/25/2011

MEMO OF TECON

Shire Attendees:	Tom Class Jim Weston Andrea Kean
FDA Attendees:	Eunice Chung-Davies

I asked Shire regarding the orientation of the proposed label on the syringe for Firazyr. The sponsor stated that the label is a clear label with black letters. Once the label is affixed to the syringe, there is a lengthwise slit so that the solution is visible through the glass. The sponsor stated that they agree to the removal of the statement as follows:

2.2 Administration Instructions

(b) (4)

The sponsor will include the change in their response to our labeling fax #6, dated August 15, 2011.

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/s/

EUNICE H CHUNG-DAVIES
08/17/2011

Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: August 15, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Shire	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: NDA 22150 Labeling Comments Fax #6

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We are currently reviewing your package insert and patient package insert submitted via email on August 11, 2011, for NDA 22150 for Firazyr (icatibant). We may have additional comments as our review proceeds. Submit a revised labeling proposal incorporating revisions shown in the attached labeling as well as your final carton and container labeling no later then noon on August 17, 2011 via email to **Eunice.Chung-Davies@fda.hhs.gov** . Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Enclosure:
PI, IFU, PPI (track change format)

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EUNICE H CHUNG-DAVIES
08/15/2011

Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: August 09, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Shire	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: NDA 22150 Labeling Comments Fax #5

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We are currently reviewing your package insert and patient package insert submitted via email on August 4, 2011, for NDA 22150 for Firazyr (icatibant). We may have additional comments as our review proceeds. Submit a revised labeling proposal incorporating revisions shown in the attached labeling no later then noon on August 12, 2011 via email to **Eunice.Chung-Davies@fda.hhs.gov** . Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Enclosure:
PI, IFU, PPI (track change format)

Initialed by: SBarnes/9AUG2011
BPorter/5AUG2011
SLimb/9AUG2011
Chowdhury/9AUG2011

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/s/

EUNICE H CHUNG-DAVIES
08/09/2011

Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: August 01, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Jerini/Shire	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: NDA 22150 Labeling Comments Fax #4

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We are currently reviewing your package insert, patient package insert, and carton and container labeling, submitted via email on July 28, 2011, for NDA 22150 for Firazyr (icatibant). We may have additional comments as our review proceeds. Submit a revised labeling proposal incorporating the comments and the revisions shown in the attached labeling no later then August 8, 2011:

The following are comments in reference to the proposed package insert:

1. Section 12.1 Mechanism of Action: While we acknowledge the cited references regarding the role of bradykinin, the statement has been modified to maintain consistency with other package inserts.

The following comments are in reference to the proposed patient package insert:

2. Convert the font to Verdana, font size 11, for improved legibility.

Please provide a response by noon on August 8, 2011 at the latest via email to **Eunice.Chung-Davies@fda.hhs.gov** . Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Enclosure:
PI, IFU, PPI (track change format)

Initialed by: SBarnes/2AUG2011
BPorter/2AUG2011
SLimb/2AUG2011
PJi/29JUL2011
JBuenconsejo/1AUG2011
YHu/2AUG2011
PPeri/2AUG2011
HRosenfeldt/2AUG2011
TRobison/2AUG2011

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EUNICE H CHUNG-DAVIES
08/02/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, August 01, 2011 1:46 PM
To: 'Class, Thomas'
Cc: Chung-Davies, Eunice
Subject: RE: NDA 22-150 Firazyr Information Request

Dear Mr. Class,

We are reviewing your application for NDA 22150 and request following information:

1. Your post-approval stability protocol for the drug product does not include 3 and 9-month time points. We request that you include these time points in the protocol for this NME.
2. In your amendment dated 20 May 2011, you state that, in order to ensure that exposures of the heavy metals [redacted] (b) (4) remain as low as reasonably achievable, Shire commits to evaluate suitable manufacturing process control strategies such as an action or alert limit to complement the specifications for these heavy metals in the drug substance. Provide estimated date for completion.
3. In your Complete Response submitted on 25 Feb 2011 to the CMC Deficiency #6a, you state that it is observed that there is greater variation in the amount of the impurity [redacted] (b) (4) [redacted] (b) (4) in the drug substance, therefore, it is proposed to retain the acceptance criterion of [redacted] (b) (4) until further manufacturing experience has been gained. Provide estimated completion date for the re-evaluation of the acceptance criterion.

Could you acknowledge the receipt and confirm that you would be providing a response no later than COB Wednesday August 3, 2011.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
08/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22150

ACKNOWLEDGE CORPORATE NAME/ADDRESS CHANGE

Shire Orphan Therapies
300 Shire Way
Lexington, MA 02421

Attention: Thomas Class, RAC
Group Director, Regulatory Affairs

Dear Mr. Class:

We acknowledge receipt on July 26, 2011, of your July 26, 2011, correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Jerini US Inc.
500 Patriot Way
Lexington, MA 02421

to

Shire Orphan Therapies Inc.
300 Shire Way
Lexington, MA 02421

for the following new drug application:

NDA 22150 for Firazyr (icatibant) injection

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have Drug Master Files (DMFs) referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their DMF(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call me, at (301) 796-4006.

Sincerely,

{See appended electronic signature page}

Eunice Chung-Davies, Pharm.D.
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

EUNICE H CHUNG-DAVIES
07/29/2011

NDA # 22-150

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 27, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Shire	Division of Pulmonary, Allergy and Rheumatology Drug Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: 781-482-9130	**Phone number:** 301-796-4006

Subject: NDA 22150 PMR Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We have the following request for information:

Below is a Post-Marketing Requirement (PMR) addressing the need for a final signed report of the kidney histopathology data from Study #JE049-0171 that you submitted in response to our May 12, 2011, information request. This information is required to support the specification of [redacted] (b) (4) at NMT [redacted] (b) (4) in your proposed drug product. Respond with a letter of intent to comply with the PMR and provide requested timelines.

1. Post-marketing Requirement: Provide a finalized signed report of the detailed kidney histopathology findings from Study # JE049-0171. The final report should include kidney histopathology data from all control and dosed groups in the study.

Your letter must include the following for each PMR/PMC:

- Study Completion: MM/YY (if applicable)
- Final Report Submission: MM/YY

In order to facilitate the review of your NDA submission, provide the requested information no later than close of business Friday, July 29, 2011 via email to Eunice.Chung-Davies@fda.hhs.gov . Your response must be officially submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Drafted by: HRosenfeldt
Initialed by: MTopper
SSeymour
SBarnes

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/s/

EUNICE H CHUNG-DAVIES
07/27/2011

Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: July 25 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Jerini/Shire	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: NDA 22150 Labeling Comments Fax #3

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We are currently reviewing your package insert, patient package insert and carton labeling, submitted on July 19, 2011, for NDA 22150 for Firazyr (icatibant). We may have additional comments as our review proceeds. Submit a revised labeling proposal incorporating these comments no later then July 28, 2011:

The following are comments in reference to the proposed package insert:

1. (b) (4)

2. Sections 6.1 and 14: The label refers to a total of (b) (4) patients vs. 223 patients enrolled in the three controlled trials. Based on the individual study reports, 223 appears to be the correct number whereas the ISS indicates a total of (b) (4) patients. Clarify the discrepancy.

3. Section 14, Figure 2: Add the sample size for each treatment arm.

The following comments are in reference to the proposed patient package insert:

4. Figure D: Revise the graphical arrow. As depicted, the arrow appears to indicate recapping of the syringe.

The following comments are in reference to the proposed carton labels and syringe label:

5. Remove (b) (4) next to the tradename.

6. On the syringe label, add information regarding the route of administration, i.e., "For subcutaneous use only."

Please provide a response by noon on July 28, 2011 via email to **Eunice.Chung-Davies@fda.hhs.gov** . Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Enclosure:
Package Insert (track change format)

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EUNICE H CHUNG-DAVIES
07/25/2011

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

DATE: July 20, 2011

SUBJECT: NDA 22150 Post Wrap Up Tecon

DRUG: Firazyr

Discussion:

Dr. Susan Limb, the CDTL for this application wished to provide Shire with an update on where the review stands and if there are any big issues remaining. Dr. Limb noted that primary reviews are near completion. The most outstanding issues are as follows:

1) Chemistry, Manufacturing, and Controls
2) PMR/PMC fax
3) Labeling (fax to be sent to the sponsor the week of the 25th of July)

The sponsor wished for some clarification regarding:

1) Whether another safety update (1 month post action) is necessary since the sponsor recently submitted a safety update at the end of June 2011 and there would not be any data to add.

    a. Post meeting update: It was confirmed with the Safety Deputy Director that the sponsor's proposal is reasonable. This has been communicated with the sponsor.

2) The sponsor indicated that they submitted a pediatric study to the IND. They would like to request for pediatric exclusivity for this application. Dr. Limb asked that the sponsor submit a request for review of their pediatric protocol (PPSR)

    a. Post meeting update: It was confirmed that the PPSR/WR is independent of the NDA action. The clock will start after the sponsor submits their request under their IND. Within 45 days, the Division will determine whether a written request will be issued. This will be communicated with the sponsor.

Drafted by: EChung-Davies
Initialed by: SLimb

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/s/

EUNICE H CHUNG-DAVIES
07/27/2011

MEMORANDUM OF TELECON

DATE: July 19, 2011

APPLICATION NUMBER: NDA 22150

BETWEEN:

Shire:

James Weston, Sr. Director Regulatory Affairs – CMC
Samantha Gao-Sheridan, Director Regulatory Affairs – CMC
Tom Class, Group Director Regulatory Affairs
Sonia Razzetti, Director QA
Mike Bauer, Assoc. Director QC
Tim Kelly, Vice President Global Supply Chain.

FDA

Susan Limb, Medical Team Lead, DPARP
Eric Duffy, Division Director, ONDQA
Prasad Peri, Branch Chief, Branch VIII, ONDQA
Alan Schroeder, CMC Lead, ONDQA
Yong Hu, Chemistry reviewer, ONDQA
Eunice Chung-Davies, Regulatory Project Manager, DPARP
Swati Patwardhan, Regulatory Project Manager-Quality, ONDQA

SUBJECT: Discussion of device testing for NDA 22150

On June 15, 2011, the Agency requested that Shire provide bench performance testing data to demonstrate the compatibility between the (b) (4) syringe with luer lock and the (b) (4) 25G needle as used in the icatibant injection product. The Agency suggested that Shire conduct the testing as required under ISO (b) (4) he purpose of this t-con was to discuss the Agency's information request.

The sponsor stated that they could commit to conducting the performance testing for the ISO standard and that they have been in discussion with (b) (4) and the contract labs for the syringe and needles. However, they expressed that they could not provide 100% assurance that they could respond to the Agency's requested due date of July 29, 2011. Shire projected that they could respond by August 12, 2011 but would work towards providing the response earlier.

The Agency requested that Shire use a sample size of 30 syringes. Shire stated that their contract labs had indicated that they typically test 10 and that a larger sample size would impact their response time. The Agency stated that they would seek additional feedback regarding this with

CDRH. However, 10 would be acceptable for our purposes.

Drafted by: EChung-Davies
Initialed by: SLimb
EDuffy

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/s/

EUNICE H CHUNG-DAVIES
08/05/2011

ERIC P DUFFY
08/05/2011

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

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Eunice Chung-Davies, RPM, DPARP, 301-796-4006

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
July 19, 2011		22-150	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Firazyr (icatibant)	6 month clock (resubmission)	respiratory	

NAME OF FIRM:	
Shire Human Genetic Therapeutics	PDUFA Date: August 25, 2011

TYPE OF LABEL TO REVIEW

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

TYPE OF APPLICATION/SUBMISSION
- ☑ ORIGINAL NDA/BLA (RESUBMISSION)
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☑ LABELING REVISION

EDR link to submission: http://darrts:9602/darrts/viewEDR.do?suppDocId=7387508

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

COMMENTS/SPECIAL INSTRUCTIONS: Dear DDMAC, This is a resubmission of an application which received a "not approveable" action in April 2008. This consult is to request DDMAC review of the PPI and IFU. The initial consult had asked for only the review of the PPI and the carton and container labels. There seems to be no medication guide (only a section 17. Patient Counseling) in this submission. The submission is completely electronic and the labeling available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0018\m1\us\annotated-draft-labeling-text-feb-2011.pdf The carton and container labels are available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0018\m1\us\draft-carton-container-labels.pdf . The PPI is available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0028\m1\us\annotated-draft-labeling-text-jul-2011.pdf
The following are the scheduled meetings for this application:
Response Review Planning Mtg: March 30, 2011
MCR Mtg: May 23, 2011
AC Meeting: June 23, 2011
Full Labeling Meeting: June 29, 2011
WU Mtg: July 15, 2011
Label Te-con: July 25, 2011
Please let me know who the reviewer and team leader for this application will be once a reviewer has been designated. Please let me know if you have any questions. Thank you.
This edited consult was requested from DDMAC for tracking purposes.

SIGNATURE OF REQUESTER
Eunice H. Chung-Davies

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☑ eMAIL/DARRTS ☐ HAND

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/s/

EUNICE H CHUNG-DAVIES
07/19/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Jerini/Shire	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: TClass@shire.com Secure Email	**Fax number:** 301-796-9728
Phone number: 781-482-9130	**Phone number:** 301-796-2300

Subject: NDA 22150 Information Request-PMR/PMC

Total no. of pages including cover:

Comments: Please confirm receipt

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We have the following comments and requests for information:

Below are two Post Marketing Requirements (PMRs) addressing your on-going evaluation of icatibant for carcinogenic potential and a proposed Post Marketing Commitment (PMC) addressing the identification and characterization of impurities in your drug product. For the PMC, refer to the pre-NDA meeting held on January 24, 2007 and the discussion regarding additional CMC comment #2 in Question 4, regarding guidelines for identification and qualification presented by Dr. Fraser, Deputy Director of ONDC, OPS, CDER, at the 2006 TIDES Conference.

Respond with a letter of intent to comply with the PMRs/PMCs and provide requested timelines.

A. Post-marketing Requirements:

   1. Submit the results of your on-going 104-week mouse carcinogenicity study of icatibant.

   2. Submit the results of your on-going 104-week rat carcinogenicity study of icatibant

B. Post-marketing Commitment:

   1. Provide the following information to identify and characterize impurities in your drug product: the structures for all the unspecified impurities observed at (b) (4) in your drug product stability studies, the structures or at least "minimal structural information" for all the unspecified impurities observed at (b) (4) in the drug product stability studies and include suitable criteria for what constitutes "minimal structural information."

Your letter must include the following for each PMR/PMC:
- Study Completion: MM/YY
- Final Report Submission: MM/YY

Please respond via email to Eunice.Chung-Davies@fda.hhs.gov by COB July 21, 2011. The response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact LCDR Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Drafted by: HRosenfeldt
TRobison
LJafari
SSeymour
YHu
PPeri

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/s/

EUNICE H CHUNG-DAVIES
07/18/2011

NDA #22-150

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2011

To: Tom Class	**From:** Eunice Chung-Davies, RPM
Company: Shire	Division of Pulmonary, Allergy and Rheumatology, Drug Products
Fax number: TClass@shire.com Secure E-mail	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006
Subject: CMC Information Request	
Total no. of pages including cover:	

Comments: Please provide a response to the request

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We have the following request for information:

> Provide bench performance testing data to demonstrate the compatibility between the [redacted] (b) (4) syringe with luer lock and the [redacted] (b) (4) 25G needle as used in the icatibant injection product. We strongly suggest that you conduct the testing as required under ISO [redacted] (b) (4)

Please provide a response as soon as possible or by July 29th, 2011 at the latest via email to Eunice.Chung-Davies@fda.hhs.gov . The response must be formally submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung-Davies/15JUL2011
Initialed by: SBarnes/15JUL2011
PPeri/15JUL2011

Finalized by: EChung-Davies/15JUL2011

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/s/

EUNICE H CHUNG-DAVIES
07/15/2011

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Jerini/Shire	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: NDA 22150 Labeling Comments #2

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We are currently reviewing your package insert, submitted on May 9, 2011 for NDA 22150 for Firazyr (icatibant). We may have additional comments as our review proceeds. Submit revised labeling incorporating these comments with the comments in our July 12, 2011, labeling fax no later then July 19, 2011:

(b) (4)

7 pages of draft labeling has been withheld in full as B (4) CCI/TS immediately following this page

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/s/

EUNICE H CHUNG-DAVIES
07/15/2011

MEMORANDUM OF TELECON (Internal Use Only)

DATE: July 12, 2011

APPLICATION NUMBER: NDA 22150

BETWEEN:

Name: **Shire:**

Susan Boynton, VP Regulatory Affairs North America and Development
James Weston, Sr. Director Regulatory Affairs – CMC
Tim Kelly, Vice President, Global Supply Chain
Sean Brennan, International Director of Quality
Gary Ward, Director Contract Manufacturing
Samantha Gao-Sheridan, Director Regulatory Affairs – CMC
Anders Lindholm, VP Pharmacovigilance and Risk Management
Howard Yuwen, Sr. Director Regulatory Affairs
Susan Bruhn, Sr. VP Regulatory Affairs
Tom Class, Group Director Regulatory Affairs

Name: **FDA**

Susan Limb, Medical Team Lead, DPARP
Eric Duffy, Division Director, ONDQA
Prasad Peri, Branch Chief, Branch VIII, ONDQA
Yong Hu, Chemistry reviewer, ONDQA
Swati Patwardhan, Regulatory Project Manager-Quality, ONDQA
Eunice Chung-Davies, Regulatory Project Manager, DPARP

SUBJECT: Follow up t-con regarding the syringe-needle presentation for NDA 22150

The Agency communicated that since our last teleconference, where we had inquired about the possibility of a fixed needle configuration for this product, the Agency has reconsidered this approach. The Agency would prefer to work with the originally proposed syringe/needle, since this is the presentation that was tested in clinical trials as well as being currently marketed outside the US. However, the Agency has noted that the sponsor submitted very limited leak testing information in the application and inquired as to the information available with regard to the types of leak testing. The sponsor responded that they would have to go back to the NDA and investigate in greater detail. The sponsor asked the Agency to provide more clarity on the performance issues that are of concern. The Agency responded that it has to do with the design of this syringe. The (b) (4) syringe (dimensions) does not conform to the ISO standard. This has led to a problem with the needles not being secure, causing leaking, breakage of the tip and

release of the needles while in use in the patient. The Agency acknowledged that the sponsor has not had any reports with the specific (b) (4) needle configuration during their clinical trials. However, Agency recognizes that the patient population was small. Shire stated that (b) (4) was not aware of the problems described above. The Agency will issue a written information request for the testing that Shire needs to perform to evaluate performance under ISO Standard (b) (4) (with a follow up teleconference).

Drafted by:	Eunice Chung-Davies
Initialed by:	SLimb
	YHu
	SPatwardhan
	ASchroeder
	PPeri
	EDuffy

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/s/

EUNICE H CHUNG-DAVIES
07/27/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 8, 2011

To: Thomas Class	**From:** Eunice Chung-Davies
Company: Shire HGT	Division of Pulmonary, Allergy and Rheumatology Drug Products
Fax number: 781-482-2958	**Fax number:** 301-796-9728
Phone number: 781-482-9130	**Phone number:** 301-796-4006

Subject: NDA 22-150 Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We request the following information:

1) Total number of icatibant syringe/needle units used to date, categorized by US and non-US use

2) Total number of self-injections to date and associated adverse events, categorized by US and non-US

3) Any reports of device failure, categorized by pre-marketing and post-marketing

In order to facilitate the review of your NDA submission, provide the requested information no later than close of business July 15, 2011 via email to Eunice.Chung-Davies@fda.hhs.gov . Your response must be officially submitted to the NDA shortly thereafter.

If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung-Davies/8JUL2011
Initaled by: SLimb/8JUL2011
SBarnes/8JUL2011

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/s/

EUNICE H CHUNG-DAVIES
07/08/2011

MEMORANDUM OF TELECON

DATE: July 6, 2011

APPLICATION NUMBER: NDA 22150

BETWEEN:

Name: **Shire:**
Susan Boynton, Vice President Regulatory Affairs
Jim Weston, Sr. Director Regulatory Affairs – CMC
Sean Brennan, International Director – QA
Sonia Razzetti, Director QA
Mike Bauer, Assoc. Director QC
Tom Class, Group Director Regulatory Affairs
Andrea Kean, Assoc. Director Regulatory Affairs - CMC.

Name: **FDA**
Badrul Chowdhury, Division Director, DPARP
Susan Limb, Medical Team Lead, DPARP
Sally Seymour, Deputy Director for Safety, DPARP
Eric Duffy, Division Director, ONDQA
Prasad Peri, Branch Chief, Branch VIII, ONDQA
Alan Schroeder, CMC Lead, ONDQA
Yong Hu, Chemistry reviewer, ONDQA
Eunice Chung-Davies, Regulatory Project Manager, DPARP
Swati Patwardhan, Regulatory Project Manager-Quality, ONDQA

SUBJECT: Calculation Error related to Total impurities for NDA 22150

Shire requested a teleconference to discuss the error in the reference standard calculations for the drug product stability and batch release testing data performed at [redacted] (b) (4) (b) (4) This is a memo to file regarding a telephone conversation on July 6, 2011, with Shire to discuss this calculation error:

1. Shire provided the summary of the issue. There was an error in the analytical assay of the impurity [redacted] (b) (4) which used the incorrect effective content for the reference standard leading to incorrect values for this impurity and the total impurities for release and stability testing. This reference standard was applied from mid 2006 to end of 2010. It is expected that the values of the total impurities will be [redacted] (b) (4) appropriate reference standard content is applied. Shire analyzed the data at a 95% confidence level and with the new impurity level and proposed that the shelf life be 18 months.

a. Shire proposed to update the NDA with the corrected impurity level. They proposed to update the CTD section.
The Agency requested that the sponsor provide the data and stated that the Agency will make all attempts to review this new data for this review cycle. Shire was requested to provide comparative data in tabular format for the old and new total impurity values. Also it was requested that Shire provide graphical representation of the stability data in order to make the review easy. The Agency requested that the sponsor provide a certification that the electronic data are accurate.

2. The Agency informed Shire that they have received a large number of complaints related to product failure for the [redacted] (b) (4) glass syringe presentation. The syringe does not meet ISO standards and is not compatible with needles that conform to ISO standards. The needle may easily detach from the syringe, leading to a safety concern. Shire stated that they were not aware of such safety issues. The Agency recommended that Shire explore alternatives to their current presentation, ideally easy substitute where no significant data need to be generated. The Agency suggested that Shire use a fixed needle presentation to mitigate the syringe-needle compatibility issue, with the syringe and needle materials being the same as for the proposed product to reduce the need for new the stability tests. Shire agreed to look into this proposal. They realized that they will have to make carton, container, and labeling changes to accommodate this new presentation. The product is being [redacted] (b) (4) hence, Shire will also need to ensure appropriate validation for the new syringe-needle presentation. It is recommended that Shire ensure that the new, fixed needle is similar in length and gauge to the currently co-packaged [redacted] (b) (4) needle. Shire expressed that they would need to discuss this issue internally and with [redacted] (b) (4) in depth before moving forward with a commitment. The Agency further noted that although their clinical studies did not show such problems, the clinical studies were in a very small population and it is uncertain what would happen if the product is used by a larger population in the U.S. It was noted that the fixed needle-syringe may be the least demanding pathway since the sponsor would not need further stability studies. Shire asked if the sponsor were to the use the fixed needle-syringe, whether this would overcome the issues of concern. The Division responded affirmatively.

Initialed by: SLimb
YHu
PPeri
EDuffy
BChowdhury

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/s/

EUNICE H CHUNG-DAVIES
08/10/2011

Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: June 12, 2011

To: Tom Class	**From:** Eunice Chung-Davies
Company: Jerini/Shire	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: Secure email	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: NDA 22150 Labeling Comments #1

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We are currently reviewing your package insert, submitted on May 9, 2011 and carton and container labels, submitted on February 25, 2011, for NDA 22150 for Firazyr (icatibant). These comments are not all-inclusive, and we may have additional comments and/or requests as we continue our review of the labels. Submit a revised labeling and carton and container proposal incorporating these comments no later then July 19, 2011. Submit a clean copy and a track changed version of the labels officially to the NDA:

The following comments are in reference to the proposed package insert:

1. Section 2, Lines 9 and 16: The dosage and administration section recommends [redacted] (b) (4) This direction is vague. Provide additional information to clarify the intended rate of injection.

2. Highlights and Section 5: [redacted] (b) (4) Clarify whether any clinical data are available to support the inclusion of these risks in the Warnings and Precautions section.

3. Section 6.1: Provide demographic information for FAST-1, FAST-2, and FAST-3. Revise the text and Table 1 to reflect the pooled population of FAST-1 and FAST-3. The current text and table indicate that 113 patients were randomized to icatibant, including patients from FAST-2. Omit adverse reactions which occurred at a greater frequency in the placebo group and round all percentages to whole numbers.

4. Section 6: Add a section on Postmarketing Experience.

5. Section 12.3: Provide appropriate references to Cmax, AUC, CL and Vss estimates

6. Section 14: Provide confidence intervals for the median values in the text. In lieu of Table 2, provide a Kaplan-Meier curve for the primary endpoint.

7. Section 17: Indicate how you plan to operationalize "training under the guidance of a healthcare professional."

8. Section 17.1: Provide instructions to ensure the sterility of the syringe tip during assembly. Clarify the instructions to ensure that the needle is properly attached to the syringe, with sufficient tightness to ensure a good seal.

9. [redacted] (b) (4) Information for Patient – Preparing the Injection Site subsection: Include a large picture of the midsection specifying areas of the abdomen where injections can be administered. The side of an abdomen as depicted may be misinterpreted for various other parts of the body.

The following comments are in reference to the proposed carton and container labels:

A. General Comments for Syringe Labels, Blister and Carton Labeling

10. Remove or decease the size of the symbol which appears on the principal display panel so that the proprietary name, established name and strength can be aligned with one another, and presented as follows :

Firazyr
Icatibant Injection
30 mg/3 mL
(10 mg/mL)

11. Because the proprietary name and the established name are presented in the same lower case font and color, the two names may be confused as one name. To distinguish the proprietary name from the established name, a parenthesis should be placed around the established name.

12. Remove the trailing zero from the statement of strength, 3.0 mL, so that it reads 3 mL.

B. Syringe Labels (commercial and sample)

13. The product name which appears in an orange color on the clear syringe label is difficult to read. Revise the color of the proprietary name and established name so that there is increased color contrast and visibility of this important information.

14 If space permits, include the route of administration on the label.

15. Include the concentration statement, i.e. 10 mg/mL, after the total drug content statement, as presented above in A10.

16. Bold or highlight the total drug content so that it is easily differentiated from the concentration statement, as presented in A10.

17. If space permits, include the ‘Rx Only’ statement on the label.

18. Decrease the font size of the manufacturer information so that other pertinent information is more prominent.

C. Blister Label

19. Remove or decease the size of the symbol which appears in the principal display paneling to decrease distraction from important information such as name and strength.

20. Increase the prominence and relocate the drug name and strength so that it is more prominently displayed on the principal display panel.

21. Remove the trailing zero in the statement of strength, 3.0 mL, so that it reads, 3 mL.

22. Relocate, increase the prominence and highlight or bold the total drug content statement so that it appears below the established name and include the concentration, 10 mg/mL, after total drug content statement as described in comment A10.

23. Revise the statement, [redacted] (b) (4) so that it reads 'Injection'.

24. Relocate the statement, 'For subcutaneous use only' so that it appears underneath the 'Injection' statement.

25. Decrease the prominence of the manufacturer information and increase the prominence of important safety information such as 'Single use product. Discard unused portion' so that this vital information is more visible to the patient and practitioner.

26. Revise the storage condition with a temperature range, i.e. Store between 2 - 25° C (36 - 77° F).

D. Carton Labeling

27. Relocate the strength and route of administration statement so that it appears underneath the proprietary name and established name, see A10.

28. Remove or decrease the size of the symbol which appears in the principal display panel, see B3, B4

29. Revise the storage condition with a temperature range, i.e. Store between 2 - 25° C (36 - 77° F).

30. List the inactive ingredients on all the cartons (single pack carton, 3-pack inner and outer cartons)

Please provide a response by July 19, 2011 via email to **Eunice.Chung-Davies@fda.hhs.gov**. Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Enclosure: Package Insert (in track change format)
Carton and Container Labels

Drafted by: Echung-Davies/8JUL2011
Initialed by: SBarnes/12JUL2011
SLimb/12JUL2011

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EUNICE H CHUNG-DAVIES
07/12/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022150

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Jerini US Inc.
Subsidiary of Shire HGT
700 Main Street
Cambridge, MA 02139

ATTENTION: Thomas Class, RAC
Group Director, Regulatory Affairs

Dear Mr. Class:

Please refer to your New Drug Application (NDA) dated October 22, 2007, received October 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Icatibant Injection, 30 mg/3 mL.

We also refer to your April 4, 2011, correspondence, received April 4, 2011, requesting review of your proposed proprietary name, Firazyr. We have completed our review of the proposed proprietary name, Firazyr and have concluded that it is acceptable.

The proposed proprietary name, Firazyr, will be re-reviewed in 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 4, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Eunice Chung-Davies at (301) 796-4006.

Sincerely,
{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
06/09/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 24, 2011

To: Thomas Class	**From:** Eunice Chung-Davies
Company: Jerini/Shire HGT	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 781-482-2958	**Fax number:** 301-796-9728
Phone number: 781-482-9130	**Phone number:** 301-796-4006
Subject: NDA 22150 Information Request	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22150, is currently under review. We have the following comments and requests for information:

1. Provide structural identification for the unidentified impurities observed at (b) (4) in the drug product stability studies. Clarify whether these unknown impurities were also observed in drug batches used for toxicology studies and justify the acceptance criteria of (b) (4) in the drug product specification. When listing drug batches known to have these impurities, list the levels of impurities observed and the associated toxicology studies in which the drug batch was used.

2. Provide the following information for the drug product batches used in the clinical studies, HGT-FIR-054 and JE049-3101:

    a) Drug product batch number
    b) Drug substance batch number
    c) Batch size
    d) Manufacturing site
    e) Batch analysis data, if not previously submitted

In order to facilitate the review of your NDA submission, provide the requested information no later than close of business (COB) June 13, 2011, in the most expeditious method. Your response must be officially submitted to the NDA shortly thereafter.

If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung-Davies/24MAY2011
Initaled by: HRosenfeldt/24MAY2011
TRobison/24MAY2011
YHu/24MAY2011
PPeri/24MAY2011
M Raggio for SBarnes/May 24, 2011

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/s/

EUNICE H CHUNG-DAVIES
05/24/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 12, 2011

To: Thomas Class	**From:** Eunice Chung-Davies
Company: Shire HGT	Division of Pulmonary, Allergy and Rheumatology Drug Products
Fax number: 781-482-2958	**Fax number:** 301-796-9728
Phone number: 781-482-9130	**Phone number:** 301-796-4006

Subject: NDA 22-150 Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We have the following comments and requests for information:

1. Tighten your drug substance specifications for [redacted] (b) (4) [redacted] (b) (4)). Provide the limit of detection and the limit of quantitation for each analytical method. Calculate total daily exposure to these metals from the maximum daily dose in your proposed label (90 mg icatibant). Ensure that daily exposures to [redacted] (b) (4) correspond to exposures that are as low as reasonably achievable. The following presentation on evolving standards for heavy metals in pharmaceuticals might be of use: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s1-10-Guest-Abernethy.ppt. Consider that many proposed safety limits are designed for oral ingestion and assume bioavailability that is [redacted] (b) (4). We consider the bioavailability of [redacted] (b) (4) via the subcutaneous route; as a result, maximum exposures calculated from an oral ingestion limit should be modified with at least a 10-fold safety margin.

2. We note that you have conducted a new 13-week rat toxicology study of subcutaneously administered [redacted] (b) (4) (Study No. JE049-0171) in order to identify a NOAEL for this degradant of icatibant and to qualify your proposed shelf-life specification of [redacted] (b) (4) [redacted] (b) (4) in the drug product. We do not concur with your estimation of the NOAEL at [redacted] (b) (4) and have the following concerns:

   a. The histopathology report shows findings of focal cortical sclerosis in the kidneys of 2/10 males and 1/10 females treated at 10 mg/kg/day. There were no similar findings in control animals. We consider this finding to be adverse.

   b. The histopathology report shows increased frequency and severity of mineral deposits in the inner and outer medulla stripes of the kidney as compared to control animals. Although there were 3 control female animals that exhibited minimal mineralization, no control animal exhibited mild mineralization in the kidney for a total of 3/10 control females exhibiting this toxicity. By contrast, 5 females treated at 10 mg/kg exhibited mild mineralization and 2 females treated at this dose level had minimal mineralization in the kidney, for a total of 7/10 females treated at 10 mg/kg exhibiting this toxicity. We consider this finding to be adverse.

   c. We note that your microscopic examination included kidney tissues from only 1/10 male rats treated at [redacted] (b) (4) mg/kg/day and 2/10 male rats treated at 1 mg/kg/day. We note further that you did not perform microscopic examination of any kidney tissues from females treated at the [redacted] (b) (4) and 1.0 mg/kg/day dose levels. Given the findings of focal cortical sclerosis and mineralization observed in the kidneys of rats treated with 10 mg/kg/day [redacted] (b) (4) it is not possible to determine a NOAEL from your submitted study. Provide historical control incidences of

these findings (mean and range) from rats of comparable age in studies of similar duration from the test laboratory over the past 5 years. Alternatively, examine kidney tissue from all male and female rats treated at (b) (4) and 1 mg/kg/day and report the incidence and severity of focal cortical sclerosis and mineralization.

d. The histopathology report shows that 3/10 male rats treated at 10 mg/kg/day exhibited findings of myocarditis while no control animals exhibited this finding. Myocarditis is not an uncommon finding in untreated male rats. However, the fact that there was a high frequency of this finding in rats treated at 10 mg/kg/day and a concomitant lack of this finding in the concurrent control requires a further examination of the historical control data pertaining to the incidence of mycarditis in studies conducted by the laboratory facility that performed Study No. JE049-0171. Provide the historical control incidence of this finding (mean and range) from rats of comparable age in studies of similar duration from the test laboratory over the past 5 years.

In order to facilitate the review of your NDA submission, provide the requested information no later than close of business Friday May 20, 2011 in the most expeditious method. Your response must be officially submitted to the NDA shortly thereafter.

If you have any questions, please contact Eunice Chung-Davies, Senior Regulatory Project Manager, at 301-796-4006.

Drafted by: HRosenfeldt/11MAY2011
Initaled by: TRobison/11MAY2011
YHu/11MAY2011
PPeri/11MAY2011
SBarnes/11MAY2011

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/s/

EUNICE H CHUNG-DAVIES
05/12/2011

NDA #22-150

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 6, 2011

To: Tom Class	**From:** Eunice Chung-Davies, RPM
Company: Shire	Division of Pulmonary and Allergy Drug Products
Fax number: Secure E-mail	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: Clinical Information Request

Total no. of pages including cover:

Comments: Please provide a response to the request

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We have the following request for information:

1. Provide a durability of response analysis by anatomic site of HAE attack for FAST-3, as presented for FAST-1 and FAST-2.

Please provide a response by May 18, 2011 in the most expeditious method. The response must be formally submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung-Davies/6MAY2011
Initialed by: SBarnes/6MAY2011
SLimb/6MAY2011

Finalized by: EChung-Davies/6MAY2011

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/s/

EUNICE H CHUNG-DAVIES
05/06/2011

NDA #22-150

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 2, 2011

To: Tom Class	**From:** Eunice Chung-Davies, RPM
Company: Shire	Division of Pulmonary, Allergy and Rheumatology Drug Products
Fax number: Secure E-mail	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006

Subject: Labeling Comments

Total no. of pages including cover:

Comments: Please provide a response to the request

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. Address the following labeling comments with regard to format and re-submit by May 10, 2011. This updated version of the labeling will be used for further labeling discussions.

Highlights

1. Extend the dashed line, which separates the headings in this section, to the end of each side of the column.

2. For the 4th bullet in Dosage and Administration, command language should be used as follows:
   Change From: [redacted] (b) (4)
   Change To: Do not administer more than 3 injections in 24 hours.

3. With regard to the Patient Counseling Information, use the following statement:

   a. See 17 for Patient Counseling information and FDA-approved patient labeling (Instructions for Use)

4. The revision date at the end of the highlights replaces the "revision" or "issued" date at the end of the Full Prescribing Information and should not appear in both places.

Full Prescribing Information: Contents

5. The headings under the Table of Contents must be identical to the headings in the Full Prescribing information.

   For Example:
   a. Change From [redacted] (b) (4)
      Change To: 8.6 Hepatic and Renal Insufficiency

6. [redacted] (b) (4) Patient Injection Instructions. The Instructions for Use should not be a subsection under the Patient Counseling section. The section should be included at the end of the package insert without numbering it as a subsection.

If you have any questions, please contact Eunice Chung-Davies, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung-Davies/28APR2011
Initialed by: SBarnes/2MAY2011

Finalized by: EChung-Davies/2MAY2011

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/s/

EUNICE H CHUNG-DAVIES
05/02/2011

NDA #22-150

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 18, 2011

To: Tom Class	**From:** Eunice Chung-Davies, RPM
Company: Shire	Division of Pulmonary and Allergy Drug Products
Fax number: Secure E-mail	**Fax number:** 301-796-9728
Phone number: N/A	**Phone number:** 301-796-4006
Subject: CP Information Request	
Total no. of pages including cover:	

Comments: Please provide a response to the request

Document to be mailed: YES xNO

Your submission dated February 25, 2011, to NDA 22-150, is currently under review. We have the following request for information:

Provide the following for study report JE049-5120:

1) All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). Provide a description of each data item in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

2) Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

3) Provide a model development decision tree and/or table, which gives an overview of modeling steps.

4) We also request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).

Please provide a response by April 22, 2011. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung-Davies/12APR2011
Initialed by: PRoy/13APR2011
SDoddapaneni/14APR2011
ABhattaram/18APR2011
YWang/18APR2011
SBarnes/12APR2011

Finalized by: EChung-Davies/18APR2011

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/s/

EUNICE H CHUNG-DAVIES
04/18/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT IRT, Division of Cardiovascular and Renal Products	FROM (*Name, Office/Division, and Phone Number of Requestor*): Eunice Chung-Davies, RPM, DPARP, 3017964006

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 15, 2011		22150	TQT study report	2-25-2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Firazyr (icatibant)	P	Respiratory/Orphan	May 23, 2011

NAME OF FIRM: Shire

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☒ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This resubmission includes a TQT study, entitled HGT-FIR-061. The study is available in global summit section 5.3.5.4. We are requesting a review prior to our Midcycle meeting since we would like to incorporate the review into our June 23, 2011 Advisory Committee meeting for this orphan drug (NME). Please contact me with any questions.

SIGNATURE OF REQUESTOR Eunice H. Chung-Davies	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

EUNICE H CHUNG-DAVIES
04/15/2011

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

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Eunice Chung-Davies, RPM, DPARP, 301-796-4006

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
March 21, 2011		22-150	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Firazyr (icatibant)	6 month clock (resubmission)	respiratory	July 14, 2011

NAME OF FIRM:	
Shire Human Genetic Therapeutics	PDUFA Date: August 25, 2011

TYPE OF LABEL TO REVIEW

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

TYPE OF APPLICATION/SUBMISSION
- ☑ ORIGINAL NDA/BLA (RESUBMISSION)
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☑ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: http://darrts:9602/darrts/viewEDR.do?suppDocId=7387508

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

COMMENTS/SPECIAL INSTRUCTIONS: Dear DDMAC, This is a resubmission of an application which received a "not approveable" action in April 2008. This consult is to request DDMAC review of the Package Insert and Carton and Container Labels. There seems to be no medication guide (only a section 17. Patient Counseling) in this submission. The submission is completely electronic and the labeling available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0018\m1\us\annotated-draft-labeling-text-feb-2011.pdf The carton and container labels are available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0018\m1\us\draft-carton-container-labels.pdf

The following are the scheduled meetings for this application:
Response Review Planning Mtg: March 30, 2011
MCR Mtg: May 23, 2011
AC Meeting: June 23, 2011
Full Labeling Meeting: June 29, 2011
WU Mtg: July 15, 2011
Label Te-con: July 25, 2011

Please let me know who the reviewer and team leader for this application will be once a reviewer has been designated. Please let me know if you have any questions. Thank you.

SIGNATURE OF REQUESTER
Eunice H. Chung-Davies

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☑ eMAIL/DARRTS ☐ HAND

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/s/

EUNICE H CHUNG-DAVIES
03/22/2011

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Eunice Chung-Davies, RPM, 301-796-4006	
DATE March 21, 2011	IND NO. N/A	NDA NO. 22-150	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT 2-25-2011
NAME OF DRUG Firazyr (icatibant)	PRIORITY CONSIDERATION 6 month clock (resubmission)		CLASSIFICATION OF DRUG Respiratory	DESIRED COMPLETION DATE 7-14-2011

NAME OF FIRM: Shire Human Genetic Therapeutics

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Dear OSE, This is a resubmission of an application which received a "not approveable" action in April 2008. This consult is to request OSE review of the Package Insert and Carton and Container Labels. There seems to be no medication guide (only a section 17. Patient Counseling) in this submission. The submission is completely electronic and the labeling available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0018\m1\us\annotated-draft-labeling-text-feb-2011.pdf The carton and container labels are available at the following link: \\cdsesub5\EVSPROD\NDA022150\\0018\m1\us\draft-carton-container-labels.pdf
The following are the scheduled meetings for this application:
Response Review Planning Mtg: March 30, 2011
MCR Mtg: May 23, 2011
AC Meeting: June 23, 2011
Full Labeling Meeting: June 29, 2011
WU Mtg: July 15, 2011
Label Te-Con: July 25, 2011
Please let me know who the reviewer and team leader for this application will be once a reviewer has been designated. Please let me know if you have any questions. Thank you.

SIGNATURE OF REQUESTER Eunice H. Chung-Davies	METHOD OF DELIVERY (Check one) ☑ MAIL/DAARTs ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

EUNICE H CHUNG-DAVIES
03/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22150

ACKNOWLEDGE – CLASS 2 RESPONSE

Jerini US Inc.
500 Patriot Way
Lexington, MA 02421

Attention: Thomas Class, RAC
Group Director, Regulatory Affairs

Dear Mr. Class:

We acknowledge receipt on February 25, 2011 of your February 25, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Firazyr (icatibant).

We consider this a complete, class 2 response to our April 23, 2008, action letter. Therefore, the user fee goal date is August 25, 2011.

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CAROL F HILL
03/15/2011
Signed for Sandy Barnes

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST**

TO *(Division/Office)*: **New Drug Microbiology Staff** ***E-mail to:*** **CDER OPS IO MICRO** ***Paper mail to:*** **WO Bldg 51, Room 4193**	FROM: Swati Patwardhan, PM, ONDQA, 301-796-4085 PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
3/4/2011		**22-150**	complete response amendment	2/25/2011

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE:
FIRAZYR (icatibant) INJECTION (b) (4)		8/25/2011	5/25/2011

NAME OF APPLICANT OR SPONSOR: SHIRE (formerly JERINI US INC)

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ☐ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY
  - ☐ PA Supplement

COMMENTS / SPECIAL INSTRUCTIONS:

NDA resubmission. The sponsor has responded to the CR letter which included micro deficiencies. Please evaluate and cc the CMC reviewers (Yong Hu and Eugenia Nashed). Steve Langille reviewed the original submission.

EDR location: \\CDSESUB1\EVSPROD\NDA022150\022150.enx

SIGNATURE OF REQUESTER: Swati Patwardhan	REVIEW REQUEST DELIVERED BY (Check one): ☒ DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND DOCUMENTS FOR REVIEW DELIVERED BY (Check one): ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

SWATI A PATWARDHAN
03/04/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: November 3, 2010

To: Thomas Class	**From:** Adele Seifried
Company: Shire Human Genetic Therapies	OND IO
Fax number: (978) 869-1542	**Fax number**: 301-796-9855
Phone number: (781) 482-9130	**Phone number:** 301-796-0535

Subject: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - IND 68,214

Total no. of pages including cover: 4

Comments:

Document to be mailed: ❑ YES ☑ NO

Executive CAC
Date of Meeting: November 2, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Adam Wasserman, Ph.D., DAAP, Alternate Member
Molly Topper, Ph.D., DPARP, Supervisor
Tim Robison, Ph.D., DPARP, Presenting Reviewer

Author of Draft: Tim Robison, Ph.D.

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

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND # 68,214
Drug Name: Firazyr® (Icatibant)
Sponsor: Shire Human Genetic Therapies

Mouse Carcinogenicity Study Protocol and Dose Selection

Background: In a second 13-week subcutaneous toxicology study (JE049-0170), CD-1 mice received icatibant at doses of 0, 5, 15, and 50 mg/kg in 0.9% physiological saline twice per week with rotation among three sites. One male animal given 50 mg/kg/dose was sacrificed for welfare reasons on day 53 due to findings of epidermal ulceration on the neck at subcutaneous injection sites. These findings were directly related to the subcutaneous administration of the test article. Sores/lesions were observed at injection sites in a dose-related manner for mice at 15 and 50 mg/kg/dose. Target tissues/organs of toxicity were the injection sites, skin + subcutis, liver, axillary and inguinal lymph nodes, stomach, urinary bladder, vagina, and Harderian glands. Findings for injection sites #1, 2, and/or 3 were observed for males and females in the mid and/or high dose groups and consisted of dose-related increased incidences of scab formation, epidermal hyperplasia, epidermal ulceration, dermal inflammatory cell infiltration, dermal fibrosis, panniculus muscle degeneration, folliculitis, and/or dermal mineralization. Findings of epidermal ulceration were generally confined to males and females in the high dose group with the exception of one male in the mid dose group. Other histopathological findings did not appear to be dose limiting with respect to identification of a MTD. The MTD was identified at 15 mg/kg/dose based upon the moribund sacrifice of one male in the 50 mg/kg/dose group due to findings of epithelial ulceration on the neck associated with subcutaneous administration of the

test article as well as findings at injection sites for the 50 mg/kg/dose group that included high incidences of scab formation, epidermal hyperplasia, epidermal ulceration, dermal inflammatory cell infiltration, dermal fibrosis, panniculus muscle degeneration, folliculitis, and/or dermal mineralization. The ulceration is a particular concern.

Executive CAC Recommendations and Conclusions:

- The Committee recommended doses of 0, 2, 5, and 15 mg/kg/dose by subcutaneous injection twice per week, based on MTD (epithelial ulceration associated with subcutaneous injections).

- The sponsor should contact the Review Division if skin lesions require dose reductions during the study.

- The committee noted that the ophthalmic examinations in the 2-year carcinogenicity study with mice are not required.

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
(b) for statistically significant or otherwise remarkable findings in the high dose group, the sponsor will need to look at the affected tissues in all of the dose groups.
(c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

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

cc:\
/Division File, DPARP
/MTopper, DPARP
/TRobison, DPARP
/CHill, DPARP
/ASeifried, OND IO

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/s/

DAVID JACOBSON KRAM
11/03/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: January 12, 2009

To: Nikhil Mehta, PhD Vice President, Global Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: Jerini US Inc. c/o Shire HGT	Division of Pulmonary and Allergy Products
Fax number: 617-613-4444	**Fax number:** 301-796-9718
Phone number: 617-613-4531	**Phone number:** 301-796-1226

Subject: NDA 22-150 - December 15, 2008 Meeting Minutes

Total no. of pages including cover: 17

Comments: Please acknowledge receipt.

Document to be mailed: ☐YES ☑NO

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type C
Meeting Category:	End of Review
Meeting Date and Time:	December 15, 2008 / 9 am
Meeting Location:	White Oak Bldg 22, Room 1417
Application Number:	NDA 22-150
Product Name:	Firazyr
Received Briefing Package	November 20, 2008
Sponsor Name:	Shire HGT on behalf of Jerini US Inc
Meeting Requestor:	Nihil Mehta/Shire HGT
Meeting Chair:	Badrul A. Chowdhury
Meeting Recorder:	Carol Hill
Meeting Attendees:	

FDA Attendees

Curtis Rosebraugh, MD, Director, Office of Drug Evaluation II (ODEII)

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary and Allergy Products (DPAP)

Sally Seymour, MD, Deputy Director of Safety, Clinical Team Leader, DPAP

Susan Limb, MD, Clinical Reviewer, DPAP

Carol Hill, MS, Regulatory Health Project Manager, DPAP

Prasad Peri, PhD, Pharmaceutical Assessment Lead, DPAI

Eugenia Nashed, PhD, CMC Reviewer, DPAI

Qian H. Li, ScD, Statistical Team Leader, Division of Biometrics II

Shire HGT attendees

Ferdinand E. Massari, M.D., Global Head, Vice President, Clinical and Medical Affairs

Nikhil Mehta, Ph.D., Vice President, Global Regulatory Affairs

Robert Mensah, Ph.D., Director, Biostatistics & Data Management

Alyssa Wyant, Assoc. Dir., Global Regulatory Affairs

Hongbin Li, Principal Statistician

Consultant

(b) (4)

1.0 BACKGROUND

Shire HGT on behalf of Jerini US Inc. submitted a meeting request dated, November 7, 2008 to obtain further clarification from the Agency regarding the Not Approvable letter dated, April 23, 2008 and also the Agency's correspondence dated, June 16, 2008. The Agency granted a Type C meeting scheduled for December 15, 2008. Shire submitted the briefing document and questions on November 20, 2008 (see section 2.0). On December 5, 2008 the Agency provided responses to the briefing document questions. In reply, Shire confirmed their attendance to the scheduled meeting in an email dated, December 11, 2008. Shire also submitted the following questions to be considered for discussion at the meeting.

1. In the 23 April 2008 Not Approvable letter you had indicated concerns regarding the validity of the primary endpoint. In your 05 December 2008 response to the Type C briefing document you have commented that the VAS validation appeared to be consistent with the requirements of the draft guidance but that this will be a review issue. We also acknowledge your position that while FAST-2 generally supports the efficacy and safety of icatibant, the post hoc analyses for FAST-1 are supportive but not acceptable for approval. We have presented several post hoc analyses for the FAST-1 study and would like confirmation that similar analyses of the primary endpoint in an additional placebo-controlled study would be acceptable to support approval.

2. Please comment on the analyses submitted regarding adjustment for rescue medication administration.

3. Additional VAS validation reports will be submitted in the Complete Response NDA amendment by the end of the month. Can the agency commit to review these VAS validation reports in advance of a February 2009 request for SPA for the confirmatory placebo-controlled study?

At the meeting held on December 15, 2008, Shire provided a slide presentation which included the additional questions submitted on December 11, 2008 and additional supportive information. These questions and the supportive information along with the pertinent discussion are listed below in Section 3.0.

2.0 AGENCY'S RESPONSES TO BRIEFING DOCUMENT QUESTIONS

Question #1

The sponsor believes that the validation studies conducted to establish the validity of the PRO diary in measuring HAE systems are consistent with the requirements of the draft PRO guidance. Does the Agency agree?

Response:

The validation studies outlined in Table 1 appear to be consistent with the requirements of the draft guidance, but whether the results of these studies confirm the validity of the PRO instrument is a review issue. As noted, some of the study reports were not submitted

in the NDA for review and, therefore, we cannot comment on their content. Based on the information provided in the original NDA, we concluded that the VAS has its limitations which may have contributed to the non-significant results of FAST-1.

Should you elect to conduct another Phase 3 efficacy and safety study, you could use the VAS as a primary efficacy variable; however, you should include additional supportive efficacy variables, such as a composite symptom score like the VDS to support the efficacy of icatibant and the validity of the VAS. Alternatively, you could consider a different primary endpoint, such as a composite symptom score and include the VAS as a key secondary endpoint to facilitate cross-study comparisons. In either case, all data to support the chosen instrument should be included at the time of submission.

Question #2

Based on the additional re-analyses conducted by the sponsor, the FAST-1 study demonstrated a statistically significant and clinically relevant treatment difference between placebo and icatibant which confirms the efficacy of Firazyr. Does the Agency agree that the results from FAST-1 and FAST-2 are adequate to support the approval of Firazyr?

Response:

No, we do not agree. While the additional efficacy analyses are supportive, post hoc analyses do not replace or outweigh the results generated from a pre-specified statistical analysis plan. An additional confirmatory study will be required to support approval of Firazyr.

Question #3

The sponsor believes the additional evidence presented based on pathophysiological rationale for use of anti-fibrinolytic agents and the comparison of FAST-2 study with literature data on natural time course of HAE attacks adequately ameliorates any concern of possible adverse effects of tranexamic acid in the treatment of acute HAE attacks. Does the Agency agree that the FAST-2 study data can be used as evidence of efficacy and safety for Firazyr?

Response:

We agree that FAST-2 generally supports the efficacy and safety of icatibant; however, based upon the totality of the information provided in the NDA, a confirmatory placebo-controlled study is required. Replicate findings of efficacy from at least two studies are required to support approval. Your application contained only one study with statistically significant results, and this issue remains the primary deficiency of the application.

3.0 ATTACHMENT WITH QUESTIONS REQUIRING FURTHER DISCUSSION

***See the handout of the slide presentation that follows and pertinent discussion.**

Type C Meeting
Firazyr, NDA 22-150

15 December 2008

Additional Question 1

- We have presented several post hoc analyses for the FAST-1 study and would like confirmation that similar analyses of the primary endpoint in an additional placebo-controlled study would be acceptable to support approval.

2

Shire

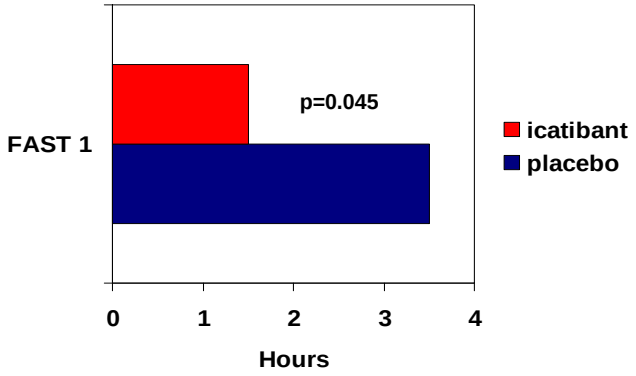
Composite Symptom VAS Score

- Composite VAS: $\frac{\sum(\text{VAS score } 1\text{-}4)}{4}$
- Accounts for multiple symptoms of HAE attacks concomitantly
- VAS scores completed by patients at each time-point in the FAST studies are included:
  - Abdominal pain
  - Skin pain
  - Skin swelling
  - Nausea

3

Shire

Time to Onset of Symptom Relief using Composite of 4 Primary Symptom VAS Scores



4

Discussion:

Shire asked the Agency to provide direction regarding reanalysis of the primary endpoints in the placebo-controlled FAST-1 study. The Agency had no specific comments on the additional analyses other than some of the analyses may provide insight into the design of the next clinical trial. For example, a composite endpoint could be something to consider in the next study. Shire noted plans to submit FAST-3 as a special protocol assessment (SPA) in February. Shire asked if the Agency recommends the use of the VAS instrument or other specific endpoints in FAST-3. The Agency stated that the choice of endpoint is Shire's. However, the Agency recommended that regardless of the primary efficacy variable, Shire should use the VAS as one of the efficacy variables. Once the SPA submission is received, guidance will be provided regarding the chosen endpoints. Shire inquired about a meeting prior to the SPA submission. The Agency recommended that Shire submit the SPA. The Agency would respond and a teleconference could be held following the SPA response, if necessary.

Additional Question 2

- Please comment on the analyses submitted regarding adjustment for rescue medication administration.

5

Handling of Rescue Medication

- Methods for censoring patients
  - Censoring patients receiving rescue medication prior to onset of symptom relief at time of rescue medication administration
  - Censoring patients receiving rescue medication prior to onset of symptom relief at last observed time point (120 h)

6

Shire

Rescue Medication Utilization Before Onset of Symptom Relief (Based on Original Primary Endpoint)

Study	Treatment Arm	
	icatibant	Comparator
FAST-1	2	10 (placebo)
FAST-2	0	7 (tranexamic acid)

7

Discussion:

The Agency commented that the rescue medication data is useful information and could be included as a sensitivity analysis or a secondary endpoint. The Agency recommended that all data be included in the main efficacy analyses, i.e. do not censor the responses in patients who receive rescue medications. The Agency inquired if the analyses will be stratified for location of HAE attack in the next trial and also inquired if consideration has been given to explore how different locations may respond. Shire stated that analysis of abdominal pain as the primary endpoint and withholding narcotics has been considered, but guidance is needed to conduct an appropriate assessment. The Agency had no particular recommendation regarding endpoints and reiterated that the choice was Shire's.

Additional Question 3

- Additional VAS validation reports will be submitted in the Complete Response NDA amendment by the end of the month. Can the agency commit to review these VAS validation reports in advance of a February 2009 request for SPA for the confirmatory study?

8

Shire

Completed Studies for VAS Validation

Validation Activity (Draft Guidance Chapter)	Report Number	Conclusions
Conceptual framework and fit to endpoint model (IV.-A.)	JE049-5105 Update: **JE049-5125***	Comprehensive information on set up of the conceptual framework and linkage of PRO claims to the concept.
Rationale for items and domains within diaries (face and content validity) (IV.-B.)	JE049-5105/**-5125*** JE049-5111 **JE049-5115*** **JE049-4104-B***	Overall face and content validity of the FAST diaries could be demonstrated.
Psychometric validation of VAS and symptom scores (validity and responsiveness using FAST trial data) (IV.-C.; VI.-D.)	JE049-5110	Demonstration of construct validity, known groups validity, clinical validity and responsiveness of VAS and symptom severity scales. Test-retest reliability detected for "abdominal pain" and "skin pain" VASs when sufficient number of stable patients was available.
Psychometric validation of VAS composite endpoints VAS-4 and VAS-3 for patients with HAE using FAST trial data (IV.-C.; VI.-D.)	**JE049-5127*** **JE049-5128***	Demonstration of test-retest reliability, construct validity, known groups validity, clinical validity and responsiveness of VAS-4 and VAS-3 composite endpoints.
Assessment of MCID (minimum clinically important difference) (IV.-C.; VI.-E.)	JE049-4102	Determination of 9mm change in VAS as MCID for onset of symptom relief.

*** New reports, to be submitted with Complete Response**

9

Discussion:

Shire also asked if the VAS validation studies should be included in the SPA or could the validation results be submitted as an amendment to the NDA. The Agency commented that the validation reports should be included in the SPA.

Shire stated that the complete response will be submitted at the end of the month to close out the new drug application (NDA). The Agency stated that the path forward would be to completely address all the deficiencies in the April 28, 2008 action letter which includes the results of an additional study and the results of the validation study. This would mean that the complete response would include the results of FAST-3.

Shire stated their plan to conduct a European self-administration study and wondered if they should submit the protocol as part of the SPA. The Agency noted that the self-administration and the FAST-3 studies are two separate trials and recommended submission of the self-administration protocol with pertinent questions to IND 68,214 for a timely review.

Regarding chemistry, manufacturing and controls, the Agency also commented that the submission should include a comparison of the strength, quality and purity of all drug products used in the new and old studies. The self-administration study should provide a side by side comparison of the drug manufacturer, drug substance, drug product, impurity profiles, and additional stability studies. A comparative analysis should be provided of the study drugs and rescue medications. The Agency inquired if the self-administration study drug is the same as the drug product used in previous studies. Shire commented that the European product is the exact same product that will be used in the FAST-3 product.

Drafted by: chill/January 7, 2009

Initialed by: Li/January 8, 2009

Nashed/January 7, 2009

Peri/January 7, 2009

Al Hakim/January 7, 2009

Limb/January 12, 2009

Seymour/January 9, 2009

Chowdhury/January 12, 2009

Finalized by: chill/January 12, 2009

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/s/

Carol F. Hill

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: December 5, 2008

To: Nikhil Mehta, PhD Vice President, Global Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Jerini US Inc. c/o Shire HGT	Division of Pulmonary and Allergy Products
Fax number: 617-613-4444	**Fax number:** 301-796-9728
Phone number: 617-613-4531	**Phone number:** 301-796-1226

Subject: NDA 22-150 - Response to questions in briefing package

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES XNO

NDA 22-150
Jerini US, Inc.
Firazyr (icatibant)

Attached are the FDA responses to your questions (in bold italics) in your November 20, 2008 meeting package regarding Firazyr. You have the option of canceling our meeting of December 15, 2008, if these answers are clear to you. If you choose to have the meeting, notify the Division of the specific questions for discussion and we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request.

Please notify the Division as soon as possible if you would like to cancel the meeting or change it to a teleconference.

Question #1

The sponsor believes that the validation studies conducted to establish the validity of the PRO diary in measuring HAE systems are consistent with the requirements of the draft PRO guidance. Does the Agency agree?

Response:

The validation studies outlined in Table 1 appear to be consistent with the requirements of the draft guidance, but whether the results of these studies confirm the validity of the PRO instrument is a review issue. As noted, some of the study reports were not submitted in the NDA for review and, therefore, we cannot comment on their content. Based on the information provided in the original NDA, we concluded that the VAS has its limitations which may have contributed to the non-significant results of FAST-1.

Should you elect to conduct another Phase 3 efficacy and safety study, you could use the VAS as a primary efficacy variable; however, you should include additional supportive efficacy variables, such as a composite symptom score like the VDS to support the efficacy of icatibant and the validity of the VAS. Alternatively, you could consider a different primary endpoint, such as a composite symptom score and include the VAS as a key secondary endpoint to facilitate cross-study comparisons. In either case, all data to support the chosen instrument should be included at the time of submission.

Question #2

Based on the additional re-analyses conducted by the sponsor, the FAST-1 study demonstrated a statistically significant and clinically relevant treatment difference

between placebo and icatibant which confirms the efficacy of Firazyr. Does the Agency agree that the results from FAST-1 and FAST-2 are adequate to support the approval of Firazyr?

Response:

No, we do not agree. While the additional efficacy analyses are supportive, post hoc analyses do not replace or outweigh the results generated from a pre-specified statistical analysis plan. An additional confirmatory study will be required to support approval of Firazyr.

Question #3

The sponsor believes the additional evidence presented based on pathophysiological rationale for use of anti-fibrinolytic agents and the comparison of FAST-2 study with literature data on natural time course of HAE attacks adequately ameliorates any concern of possible adverse effects of tranexamic acid in the treatment of acute HAE attacks. Does the Agency agree that the FAST-2 study data can be used as evidence of efficacy and safety for Firazyr?

Response:

We agree that FAST-2 generally supports the efficacy and safety of icatibant; however, based upon the totality of the information provided in the NDA, a confirmatory placebo-controlled study is required. Replicate findings of efficacy from at least two studies are required to support approval. Your application contained only one study with statistically significant results, and this issue remains the primary deficiency of the application.

If you have any questions, you may contact Ms. Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted by:	chill/December 4, 2008
Initialed:	Barnes/December 4, 2008
	Limb/ December 4, 2008
	Seymour/ December 4, 2008
	Chowdhury/December 5, 2008
Finalized:	chill/December 5, 2008

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/s/

Carol F. Hill
12/5/2008 05:29:43 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-150

Jerini US Inc.
c/o Shire Human Genetic Therapies
700 Main Street
Cambridge, MA 02139

Attention: Nikhil Mehta, Ph.D.
Vice President, Global Regulatory Affairs
Authorized U.S. Agent

Dear Dr. Mehta:

Please refer to your Investigational New Drug Application (IND)/New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Firazyr (b) (4), 30 mg/3mL.

We also refer to your November 7, 2008, request for a meeting to obtain further clarification regarding the Not Approvable letter dated April 23, 2008 and the Agency's correspondence dated June 16, 2008.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: December 15, 2008
Time: 9-10 am
Location: Food and Drug Administration
Center for Drug Evaluation and Research
White Oak, Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

CDER Participants (tentative list):
Curtis Rosebraugh, MD, Director, Office of Drug Evaluation II (ODEII)
Leah Ripper, Associate Director Regulatory Affairs, ODEII
Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary and Allergy Products (DPAP)
Sally Seymour, MD, Deputy Director of Safety, Clinical Team Leader, DPAP
Susan Limb, MD, Clinical Reviewer, DPAP
Timothy W. Robison, PhD, Acting Pharmacology/Toxicology Team Leader, DPAP
Molly Shea, PhD, Pharmacology/Toxicology Team Leader, DPAP
Carol Hill, MS, Regulatory Health Project Manager, DPAP

Ali Al Hakim, PhD, Chief, Branch 2, Division of Pre-Marketing Assessment I (DPAI)
Prasad Peri, PhD, Pharmaceutical Assessment Lead, DPAI
Eugenia Nashed, PhD, CMC Reviewer, DPAI
Wei Qiu, PhD, Acting Clinical Pharmacology Team Leader, Division of Pharmacology 2 (DCP2)
Partha Roy, PhD, Clinical Pharmacology Reviewer, DCP2
Qian H. Li, ScD, Statistical Team Leader, Division of Biometrics II

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at carol.hill@fda.hhs.gov so that the security staff may prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Carol Hill, x 61226 or the division secretary, Ms. Alston, x 62300.

Provide the background information for this meeting (three copies to the NDA and 14 desk copies to me) on or before November 21, 2008. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by November 21, 2008, we may cancel or reschedule the meeting.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Hill, M.S.
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Carol F. Hill
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Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF NEW DRUGS

FACSIMILE TRANSMITTAL SHEET

DATE: 10/22/08

To: Glen Park	**From:** **Sam Habet, RP.h., Ph.D.** **Senior Clinical Pharmacologist and Science Policy Analyst (Detail)** **OND**
Company: Jerini AG	OND IO sayed.alhabet@fda.hhs.gov
Fax number: 212-681-2105	**Fax number:** 301-796-9855
Phone number: 212-681-2100	**Phone number:** 301-796-1496

Subject: Executive Carcinogenicity Committee Meeting Minutes (October 21, 2008)
Submission: IND 68,214 and NDA 22-150
Date of submissions: September 8, 2008 (IND) and October 22, 2007 (NDA)
Drug Name: Icatibant Acetate (Firazyr)

Total no. of pages including cover: 5 + 1 (signature page) = 6

Comments:

Document to be mailed: ☐ YES ☑ NO

Executive CAC
Date of Meeting: October 21, 2008

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Wendy Schmidt, Ph.D., DAIOP, Alternate Member
Luqi Pei, Ph.D., DPAP, Acting Team Leader
Molly Shea, Ph.D., DPAP, Presenting Reviewer

Coordinator: Sam Habet, R.Ph., Ph.D., OND IO, Senior Clinical Pharmacologist/ Science Policy Analyst (Detail)

Author of Minutes: Molly Shea, Ph.D.

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

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format, Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND#: **68, 214 (September 8, 2008)**
NDA#: **22-150 (October 22, 2007)**
Drug Name: Icatibant Acetate (Firazyr)
Sponsor: Jerini AG

Background: Icatibant acetate is being developed for the treatment of patients with hereditary angioedema (HAE) who are 18 years old and older. In Type I (quantitative deficiency) and Type II (qualitative deficiency) HAE, a deficiency of C1-esterase inhibitor (C1-INH), results in an increased release of bradykinin (BK). BK binds to the bradykinin type-2 receptor (B_2) to trigger activation of many cascades leading to vasodilatation, increased vascular permeability and smooth muscle cell contraction, resulting in the increased vascular permeability and acute inflammation observed in HAE patients. The anticipated clinical dosing of icatibant in patients having an HAE attack is 30 mg/day up to 3 times daily SC. Therefore, the maximum recommended human dose (MRHD) of icatibant is 90 mg/day, which is associated with AUC levels of 14.27 mcg*h/mL (extrapolated AUC levels observed in elderly females treated with 30 mg/day SC dosing).

Icatibant is a synthetic decapeptide with potent and selective B_2 receptor antagonist activity that binds to the B_2-receptor with similar affinity as BK. Icatibant binding at the

B_2 receptor inhibits BK induced processes and is hypothesized to contribute to the decrease of vascular permeability and acute inflammation observed in HAE patients.

Absorption, distribution, metabolism and elimination (ADME) studies were conducted in the rat. In the rat, icatibant is metabolized to the active metabolites M1 (b) (4) and M2 (b) (4) by hydrolysis of icatibant's peptide backbone, thought to be catalyzed by peptidases. The M1 is formed at >90% and 70% in man and rat, respectively. M2 is formed up to ~9% in rat and in up to ~75% in humans. After SC administration in rats, distribution studies showed that icatibant (or its metabolites) is distributed into the kidneys, liver, urinary bladder, lungs and spleen 1 hour post-dose and is still detectable in the liver, kidneys, spleen, bone marrow, adrenals and injection sites at 24-hours post-dose. After repeat SC dosing in rats, icatibant is rapidly distributed and metabolized with the M2 metabolite appearing from 0.2 to 3 hours post-dose. Neither icatibant nor M2 accumulated after repeat dosing in male and female rats up to 13-weeks dosing. The half-life was more than 5 hours after 26 µg/kg SC in rats and terminal half-life was over 6 days in rats after 10 µg/kg, SC. There were no gender differences observed in rats in the systemic exposures of males and females. Serum protein binding of icatibant was low with 44 and 49% in man and rat, respectively.

Neither icatibant nor the M1 or M2 metabolites is metabolized by human hepatocytes or microsomes. Additionally, icatibant is not an inducer of CYP450 isozymes. Based on excretion studies, the primary route of elimination after SC administration of icatibant is via the kidneys in rats (~61%) with small amounts excreted in the feces (8.0% to 33%).

Jerini completed a full genetic toxicity battery assessment for icatibant. Icatibant did not induce genetic toxicity in the presence or absence of metabolic activation in the bacterial reverse mutation assays or *in vitro* mammalian chromosomal aberration studies or micronuclei formation in *in vivo* assays under the conditions tested.

The sponsor sought concurrence for dose selection and regimen for the 104-week carcinogenicity study in male rats.

Male Rat Carcinogenicity Study

The sponsor proposed a standard 2-year carcinogenicity study in male Wistar rats at SC doses of 0 (vehicle, saline), 1, 3 and 6 mg/kg/day based on a MTD approach and on the secondary PD actions of icatibant. The sponsor considered the study results from the 13-week repeat dose rat study, the 26-week repeat dose rat study and the combined rat toxicity and fertility study to support their proposed doses. The 13-week repeat dose rat SC study (Study no. JE049-0160; doses of vehicle, 10, 20 or 30 mg/kg/day) resulted in treatment-related changes in adrenal glands, injection sites, thymus, epididymides, prostate glands, seminal vesicles and testes in males. A significant decrease in body weight gains exceeding 10% in males was also observed at all doses. In the combined rat toxicity and fertility study (JE049-0108) at daily doses of 0, 1, 3 and 10 mg/kg/day SC, the sponsor concluded that body weights and body weight gains in males were equal to or greater than control males throughout the 13-week treatment period. Data from the 26-

week rat study showed that the decrease in male body weight gains were related to the pharmacological effects of icatibant reducing testosterone levels. The sponsor stated that the 10 mg/kg/day icatibant dose in male rats will result in a significant reduction in circulating plasma testosterone and hence may be unacceptable for selection for administration for the duration of a carcinogenicity study. Furthermore the sponsor stated that although a dose dependent reduction in circulating testosterone will occur, selection of dose levels of 1, 3 and 6 mg/kg/day will have less negative impact on animal body weight gain. From these data, the sponsor selected doses at 1, 3 and 6 mg/kg/day in males.

Based on a detailed review of the 26-week repeat dose SC toxicity study in the Wistar rat study, the dose-limiting toxicity was injection site reactions (fibrosis, ulcerations, degeneration of muscles and hemorrhage) in males. The MTD was 3 mg/kg/day in males based on tolerable body weight loss and injection site reactions and reduced incidence of effects observed in the thymus, adrenals, liver, hematopoietic tissues, and male reproductive organs at this dose. The decrease in relative body weight at 3 mg/kg/day (6%) was tolerable for males through the 26-week dosing period and thus was not a dose limiting toxicity. The sponsor did not evaluate the 6 mg/kg/day dose of icatibant in their rat studies. Based on extrapolation of the body weight data, at 6 mg/kg/day a decrease in body weight would be approximately -10% after 26 weeks of SC administration. At the 6 mg/kg/day dose, it is not known whether injection site toxicity would be substantial. At the proposed carcinogenicity doses of 1, 3 and 6 mg/kg/day in male rats, the expected exposure margins would be 0.17-, 0.52- and 1.03-fold, respectively, at the MRHD.

Executive CAC Recommendations and Conclusions:

Male Rat:

- The Committee concurred with the proposed doses of 0 (VC), 1, 3, and 6 mg/kg/day for male rats, by SC injection and with injection site rotation, based on MTD (severe local toxicity).
- If a survival problem occurs during the study, the sponsor should immediately contact the reviewing division at the FDA prior to terminating any animals or changing any dosing.

Female Rat:

- The Committee noted that the June 10, 2008 recommendation of the top dose of 10 mg/kg/day Icatibant may be revised to 6 mg/kg/day, SC in female rats. This revised recommendation was based on the significant injection site toxicity observed at the 10 mg/kg/day dose in females in the 26-week repeat-dose rat study submitted in support of the proposed male rat doses.

General comments:

- The potential carcinogenicity of the M2 metabolite will not be addressed by the proposed study. The sponsor should conduct and submit for review a dose ranging study for M2 for FDA concurrence on dose selection and consider adding an arm to the proposed carcinogenicity study. If a separate arm is not added, another carcinogenicity study on the M2 metabolite will be needed.
- The sponsor should omit ophthalmic exam and urine measurements.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

/Division File, DPAP
/LPei, DPAP
/MShea, DPAP
/CHill, RPM, DPAP
/DJacobson-Kram, OND IO
/AJacobs, OND IO
/SHabet, OND IO

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/s/

Sayed Al-Habet
10/22/2008 03:49:24 PM
BIOPHARMACEUTICS

Abby Jacobs
10/22/2008 03:51:39 PM
PHARMACOLOGIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: June 16, 2008

To: Glen D. Park, PharmD Authorized US Agent	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: Jerini US Inc. c/o Target Health	Division of Pulmonary and Allergy Products
Fax number: 212-681-2105	**Fax number:** 301-796-9728
Phone number: 212-681-2100	**Phone number:** 301-796-1226

Subject: NDA 22-150 – Responses for End of Review Meeting on June 17, 2008

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES XNO

NDA 22-150
Jerini US Inc
Firazyr (icatibant)

Attached are the FDA responses to your questions (in bold italics) in your May 29, 2008 meeting package regarding Firazyr. You have the option of canceling our meeting of June 17, 2008, if these answers are clear to you. If you choose to have the meeting, notify the Division of the specific questions for discussion and we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request.

Please notify the Division as soon as possible if you would like to cancel the meeting or change it to a teleconference.

Question #1
To what extent, if any, did the Division review the contents of the amendment submitted on February 18, 2008 (eCTD sequence 0004)?

FDA Response:

The updated efficacy and safety information from the open-label extension phases of both pivotal studies as well as the additional efficacy analyses included in the February 18, 2008, amendment were reviewed and considered supportive evidence of icatibant's safety in the treatment of acute HAE attacks. However, the efficacy data from the extension studies has limitations because the data is unblinded and uncontrolled. Similarly, the additional efficacy analyses have limitations as they are post-hoc analyses.

Question #2
The second sentence of Point 1 of the deficiencies refers to the "uncertain efficacy of the comparator drug, tranexamic acid." Inasmuch as icatibant was demonstrated to be superior to tranexamic acid in Study JE049#2102, and as discussed in detail in the amendment submitted on February 18, 2008, it is neither scientifically nor legally necessary for a comparator drug to have demonstrated efficacy so long as it is not worse than placebo in a superiority study. Is it the Division's view that tranexamic acid is worse than placebo? If so, why? If the Division agrees that tranexamic acid is not worse than placebo, can you help us to understand why lack of efficacy of tranexamic acid would undermine the findings in a superiority study?

FDA Response:

The Division does not view tranexamic acid as inferior or superior to placebo, as its efficacy and safety relative to placebo have not been established. The uncertain efficacy of tranexamic acid creates questions in the only study in which icatibant was statistically superior to a comparator.

Question #3

What are the "concerns regarding the validity of the primary endpoint used in both studies"? As you are aware, the primary endpoint for the FAST-1 study was the subject of a special protocol assessment and the then-responsible Division director said explicitly that the primary endpoint was acceptable. What has changed since then to make the Division depart from this binding commitment?

FDA Response:

As discussed at the January 24, 2007, Pre-NDA meeting (Meeting Minutes dated February 22, 2007), establishing the validity of the VAS tool used to define the primary endpoint was a critical component of the clinical development program and was considered a review issue. In general, the information provided did not clearly demonstrate that the VAS was an accurate measure of patient symptoms, thus the validity of the VAS is questioned.

Question #4

On the same point as above, is the Division questioning the use of VAS to measure symptoms during an acute attack of HAE?

FDA Response:

The VAS as a measure of HAE attack symptoms appears to have its limitations as noted above and may have contributed to the non-significant results in your confirmatory clinical trial. Should you elect to conduct another Phase 3 efficacy and safety study, you could use the VAS as a primary efficacy variable; however, you should include additional supportive efficacy variables, such as a composite symptom score like the VDS to support the efficacy of icatibant and the validity of the VAS. Alternatively, you could consider a different primary endpoint, such as a composite symptom score and include the VAS as a key secondary endpoint to facilitate cross-study comparisons.

Question #5

Could the Division explain its reasons for raising the concern in Point 3?

FDA Response:

As discussed in the January 24, 2007 Pre-NDA meeting (Meeting Minutes dated February 22, 2007), the product label should reflect the method of administration used in the clinical studies. Given the potentially life-threatening aspects of HAE and the fact that early intervention with self-administration may affect the efficacy and safety profile of icatibant, clinical data are required to support self-administration. Because additional clinical trial data are required to establish the efficacy of icatibant, we recommend inclusion of self-administration into the clinical trial design.

Question #6

Could the Division explain its reasons for raising the concern in Point 5?

FDA Response:

Your PK/PD modeling approach of using bradykinin challenge in healthy subjects for Phase 3 dose selection appears inadequate. With the use of this biomarker, the Phase 3 dose selected was not efficacious based on the clinical endpoint defined by the VAS. The possible reasons are: (a) uncertainty about the relationship between bradykinin challenge and VAS; (b) unaccounted larger variability in VAS than bradykinin challenge, leading to an underpowered design; and (c) given the lower plasma bradykinin level (15 pM – 30 pM) after bradykinin challenge in a healthy subject compared to that in a patient during an acute HAE attack (>50 pM), the dose based on PK/PD modeling may be an underestimate of the dose for HAE patients. The limitations associated with bradykinin challenge may have contributed to the non-significant results in your confirmatory clinical trial. Therefore, we encourage you to support your dose selection based on clinical endpoints or valid surrogate endpoints.

W e recognize the limited population of hereditary angioedema patients; therefore, if you establish the efficacy of icatibant 30mg, then additional dose selection data may not be necessary.

If you have any questions, you may contact Ms. Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by:	chill/June 12, 2008
Initialed:	Barnes/June 12, 2008
	Roy/June 12, 2008
	Qiu/June 12, 2008
	Limb/June 12, 2008
	Seymour/June 12, 2008
	Chowdhury/June 12, 2008
Finalized:	chill/June 16, 2008

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/s/

Carol F. Hill
6/16/2008 10:38:24 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: June 11, 2008

To: Glen Park	**From:** Adele Seifried
Company: Jerini AG	OND IO
Fax number: (212) 681-2105	**Fax number:** 301-796-9855
Phone number: (212) 681-2100	**Phone number:** 301-796-0535

Subject: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - IND 68,214

Total no. of pages including cover: 6

Comments:

Document to be mailed: ❑ YES ☑ NO

Executive CAC
Date of Meeting: June 10, 2008

Committee: David Jacobson Kram, OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Lois Freed, Ph.D., DNP, Alternate Member
Timothy McGovern, Ph.D., DPAP, Team Leader
Molly Shea, Ph.D., DPAP, Presenting Reviewer

Author of Minutes: Molly Shea, Ph.D.

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

The Committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogenicity bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND # 68, 214
Drug Name: Icatibant Acetate (Firazyr)
Sponsor: Jerini AG

Background: Icatibant acetate is a synthetic decapeptide being developed for the treatment of patients with hereditary angioedema (HAE) who are 18 years old and older. In Type I (quantitative deficiency) and Type II (qualitative deficiency) HAE a deficiency of C1-esterase inhibitor (C1-INH) results in an increased release of bradykinin (BK). BK binds to the bradykinin type-2 receptor (B_2) to trigger activation of many cascades leading to vasodilatation, increased vascular permeability and smooth muscle cell contraction, resulting in the increased vascular permeability and acute inflammation observed in HAE patients. The anticipated clinical dosing of icatibant in patients having an HAE attack is 30 mg/day up to 3 times daily SC. Therefore, the maximum recommended human dose (MRHD) of icatibant is 90 mg/day, which is associated with AUC levels of 14.27 mcg*h/mL (extrapolated from AUC levels observed in elderly females treated with 30 mg/day SC dosing).

Absorption, distribution, metabolism and elimination (ADME) studies were conducted in the mouse and rat. However, these studies were limited for the mouse. In both the mouse and the rat, icatibant is metabolized to the active metabolites M1 [Icatibant (1-5)] and M2 [Icatibant (7-10)] by hydrolysis of icatibant's peptide backbone, thought to be induced by peptidases. M1 is formed at >90%, ~50% and 70% in human, mouse and rat, respectively. M2 is formed in rat ~9% and in human ~75%. After repeat SC dosing in rats, icatibant is rapidly distributed and metabolized with the M2 metabolite appearing from 0.2 to 3 hours post-dose. Neither icatibant nor M2 accumulated after repeat dosing in male and female rats up to 13-weeks dosing as was observed in the NDA. The biological half-life was more than 5 hours after a 26 µg/kg SC dose in rats and terminal half-life was over 6 days in rats after 10 µg/kg, SC. There were no differences observed in rats in the

systemic exposures of males and females. Serum protein binding of icatibant was low with 44 and 49% in human and rat, respectively. No serum protein data are available for the mouse.

Neither icatibant nor the M1 or M2 metabolites is metabolized by human hepatocytes or microsomes. Additionally, icatibant is not an inducer of CYP450 isozymes. Based on excretion studies, the primary route of elimination after SC administration of icatibant is via the kidneys in mice (~97.1%) and rats (~61%) with small amounts excreted in the feces (8.0% to 33%).

Jerini completed a full genetic toxicity battery assessment for icatibant. Icatibant did not induce genetic toxicity in the presence or absence of metabolic activation in the bacterial reverse mutation assays or *in vitro* mammalian chromosomal aberration studies or micronuclei formation in *in vivo* assays under the conditions tested.

The sponsor sought concurrence for dose selection and regimen for two 104-week carcinogenicity studies in mice and rats.

Mouse Carcinogenicity Study or Mouse Dose Selection

The sponsor proposed a standard 2-year carcinogenicity study in CD-1 mice at SC doses of 0 (vehicle control), 10, 30 and 100 mg/kg/day. Three injections sites are to be used with daily rotation. The sponsor considered icatibant doses up to 100 mg/kg/day in mice as the maximum tolerated dose based on local tolerance and stated that this dose provides an exposure which is at least ≈7 times that reached in the clinic at the MRHD of 90 mg/day.

Based on a detailed review of the dose-range finding 13-week SC mouse study, the dose-limiting toxicity was injection site reaction with hemorrhage, ulceration and necrosis observed at multiple injection sites in males and females that increased in incidence and severity at the 100 mg/kg/day dose. Of note, mice were dosed with 100 mg/kg/day for only 4 weeks (from Weeks 9 to Weeks 13) and severe local reactions were observed for this truncated dosing interval compared to the 13-week dosing up to 50 mg/kg/day. Therefore, the MTD was exceeded at 100 mg/kg/day SC doses based on the injection site toxicity. The MTD was determined to be 50 mg/kg/day based on tolerable levels of injection site reaction.

Rat Carcinogenicity Study or Rat Dose Selection

The sponsor proposed two alternative dosing regimens for the 2-year rat carcinogenicity study at doses that were based on the MTD, pharmacodynamic action of icatibant and on previously conducted repeat dose toxicity studies in the dog which used similar alternative dosing regimens. These regimens alternated seven injection sites and were presented as follows:

Option A: 0 (0.9% physiological saline-VC), 3 mg/kg t.i.d (twice weekly), 10 mg/kg t.i.d (twice weekly) and 10 mg/kg/day

Option B: 0 (0.9% physiological saline-VC), 10 mg/kg t.i.d. (twice weekly), 3.3 mg/kg/day and 10 mg/kg/day

The sponsor proposed a HD of 10 mg/kg/day of icatibant in each of the alternative dosing regimens. The two dosing regimens incorporated daily and intermittent dosing but differed in

whether the dose response relationship of any eventual findings would be investigated based on daily or intermittent dosing. The sponsor stated that 10 mg/kg t.i.d to be administered twice weekly allows for a greater daily dose while allowing for sufficient rotation of injection sites.

Based on a detailed review of the dose-range finding 13-week SC Wistar rat study, the dose-limiting toxicities were reduced body weight gain or body weight loss in all treated male groups and high dose females and injection site reactions in males and females. The MTD was 10 mg/kg/day in females based on no change in group mean body weight gains, no injection site reactions and reduced incidence of effects observed in the thymus, adrenals and female reproductive organs at this dose. For males, the MTD was not identified based on male body weight gain reduction exceeding 10% in all icatibant treated animals and injection site reaction at doses > 10 mg/kg/day.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee recommended daily doses of 0 (VC), 5, 15, and 50 mg/kg/day, by SC injection and injection site rotation in males and females, based on an MTD criterion (severe local toxicity).

Rat:

- The Committee concluded that the data were insufficient to make dose recommendations for male rats as all tested doses exceeded the MTD based on significant reductions in body weight gain in comparison to control animals. The proposed alternative dosing regimens (t.i.d dosing, 2 times per week) are not supported by the 13-week repeat dose rat study which administered drug on a daily basis. Due to the absence of TK data in the draft study report for the dose-ranging study, rat to human exposure comparisons can not be calculated.

- The Committee recommended daily doses of 0 (VC), 1, 3, and 10 mg/kg/day for female rats, by SC injection with site rotation, based on MTD (severe local toxicity).

- If a dosing regimen other than daily dosing is desired, the range-finding study should be conducted using that regimen.

General comments:

- The sponsor should contact the Division prior to terminating any groups or making any dose adjustments.
- The proposed hematological and urine measurements should be omitted.
- TK evaluations are not needed beyond 6 months.

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

cc:\

/Division File, DPAP
/TMcGovern, DPAP
/MShea, DPAP
/CHill, RPM, DPAP
/ASeifried, OND IO

Linked Applications	Sponsor Name	Drug Name
IND 68214	JERINI AG	Firazyr

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/s/

DAVID JACOBSON KRAM
06/11/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-150

Jerini US Inc.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm.D.
Authorized U.S. Agent

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Firazyr 30 mg [redacted] (b) (4).

We note your email dated, May 6, 2008, requesting an End of Review Conference. We also refer to your electronic correspondence, dated and received, May 15, 2008, regarding your request. The purpose of the meeting is to seek information to plan an appropriate course of action in reference to the Not Approvable letter issued on April 23, 2008.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). As previously discussed, the meeting is scheduled for:

Date: June 17, 2008
Time: 1 pm to 2:30 pm
Location: Food and Drug Administration
Center for Drug Evaluation and Research
White Oak, Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Participants (tentative):
Office of Drug Evaluation II
Curtis Rosebraugh, M.D., Director

Division of Pulmonary and Allergy Participants
Badrul A. Chowdhury, M.D., Ph.D., Director
Sally Seymour, M.D., Clinical Team Leader
Susan Limb, M.D., Clinical Reviewer
Anthony Durmowicz, M.D., Clinical Reviewer
Timothy McGovern, Ph.D., Pharmacology/Toxicology Supervisor

Molly Shea, Ph.D., Pharmacology/Toxicology Reviewer
Carol Hill, M.S., Regulatory Project Manager

Division of Pre-Marketing Assessment I
Ali Al-Hakim, Ph.D., Chief, Branch II
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead
Eugenia M. Nashed, Ph.D., CMC Reviewer

Division of Clinical Pharmacology
Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader
Partha Roy, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics II
Qian H. Li, Sc.D., Statistical Team Leader

New Drug Microbiology Staff
Anastasia Lolas, Ph.D., Microbiology Reviewer

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at carol.hill@fda.hhs.gov so the security staff may have time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Carol Hill, extension 61226; the division secretary, extension 62300.

As previously discussed, the background information for this meeting (three copies to the NDA and 15 desk copies to me) will be provided on June 3, 2008. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 3, 2008, we may cancel or reschedule the meeting.

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Hill, M.S.
Regulatory Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Carol F. Hill
5/21/2008 08:03:47 AM

Ripper, Leah W

From: Laska, Susan F
Sent: Wednesday, April 23, 2008 3:06 PM
To: Adams, Shawnte L; Ripper, Leah W
Subject: RE: EER for DNA 22-150 - Action Planned on Wednesday

Leah,

Based on the inspection results [redacted] (b) (4) both sites are unacceptable at this time.

Susan Laska, CDER/OC
Acting Team Leader International Compliance Team
301/796-3214
Susan.Laska@FDA.HHS.GOV

From: Adams, Shawnte L
Sent: Tuesday, April 22, 2008 7:58 AM
To: Ripper, Leah W
Cc: Barnes, Sandy L (CDER); Hill, Carol; Laska, Susan F
Subject: RE: EER for DNA 22-150 - Action Planned on Wednesday

Leah,

The two testing labs [redacted] (b) (4) that were added late in the review will not be scheduled for inspection prior to April 23, 2008 or the PDUFA date. [redacted] (b) (4) has never been inspected by FDA before and [redacted] (b) (4) last inspection was [redacted] (b) (4). Office of Compliance cannot provide a GMP assessment of either of these facilities without a GMP inspection. I know that ORA/DFI is working on scheduling the inspections of these facilities however I do not have confirmed inspection dates.

I will have my Acting Team Leader Susan Laska review the inspection recommendations for [redacted] (b) (4) so that we can have those compliance assessment entered into EES.

Thank you,

Shawnte L. Adams
Program Analyst
Office of Compliance
Division of Manufacturing and Product Quality
International Compliance Team
301-796-3193 (Office)
301-847-8738 (Fax)
General Foreign Inspection questions should be directed to: cderict@fda.hhs.gov
FWAP: Tuesday and Thursday

From: Ripper, Leah W
Sent: Monday, April 21, 2008 1:36 PM
To: Adams, Shawnte L
Cc: Barnes, Sandy L (CDER); Hill, Carol
Subject: EER for DNA 22-150 - Action Planned on Wednesday

Shawnte,
It looks like we will have to take an action on NDA 22-150 on Wednesday, April 23, because Dr. Rosebraugh will be out after that for medical reasons. Please keep us updated on the status of the pending inspections.

Regardless of the outcome of the inspections, we will be issuing an NA letter, the applicant will have to do additional clinical trials before the application can be approved. So, we will issue the letter even if all the inspections have not been completed. We just need to know what their status is.

Lee

Lee W. Ripper
Associate Director for Regulatory Affairs
Office of Drug Evaluation II
Bldg 22, Room 3218, Mail Stop 3105
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903
Phone: 301-796-1282 / Fax: 301-796-9717
Mailing Address: FDA, CDER, OND, ODE II IO
5901-B Ammendale Road
Beltsville, MD 20705-1266
Email: leah.ripper@fda.hhs.gov

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **April 22, 2008**

To: **Glen Park, Pharm D** **Authorized US Agent**	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: **Jerini US Inc.** **c/o Target Health**	Division of Pulmonary and Allergy Products
Fax number: 212-681-2105	**Fax number:** 301-796-9728
Phone number: 212-681-2100	**Phone number:** 301-796-1226

Subject: **NDA 22-150 – Agency's Response to a Request to Change Official Minutes**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ YES ☑ NO

NDA 22-150
Jerini U.S., Inc.
Firazyr

We acknowledge your submission dated, April 14, 2008, requesting changes in the official March 5, 2008 meeting minutes. We have considered the concerns in your correspondence and conclude that there are no significant differences in Jerini's and the Agency's understanding of the content of the minutes to effect a change to the official meeting minutes. Your request is documented as an official record to the application.

If you have any questions, contact Carol Hill, Regulatory Project Manager at 301-796-1226.

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/s/

Carol F. Hill
4/22/2008 01:53:14 PM
CSO

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type C
Meeting Category:	90-Day Conference
Meeting Date and Time:	March 5, 2008
Meeting Location:	White Oak Building, Rm. 1417
Application Number:	NDA 22-150
Product Name:	Firazyr
Received Briefing Package	February 25, 2008
Sponsor Name:	Jerini U.S., Inc.
Meeting Requestor:	Glen Park, PharmD
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Carol Hill, MS
Meeting Attendees:	

FDA

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary and Allergy Products
Sally Seymour, MD, Clinical Team Leader, Division of Pulmonary and Allergy Products
Qian H. Li, ScD, Statistical Team Leader, Division of Biometrics
Yaning Wang, PhD, Pharmacometrics Team Leader, Office of Clinical Pharmacology, Pharmacometrics Staff
Nitin Mehrotra, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology, Pharmacometrics Staff

Sponsor

Nancy L. Buc, JD, Counsel, Buc & Beardsley

Jochen Knolle, PhD. Chief Scientific Officer, Head of R&D, Jerini AG

Glen Park, PharmD, Regulatory Consultant & U. S. Agent, Target Health

Jens Schneider-Mergener, PhD, CEO, Jerini AG

Bernd Rosenkranz, MD, VP, Clinical Development Jerini

(b) (4)

Michael J. Vivion, PhD, Meeting Recorder

1.0 BACKGROUND

Jerini US, Inc. submitted a New Drug Application (NDA) dated, October 22, 2007, received, October 26, 2007 for icatibant (Firazyr), a bradykinin type-2 receptor antagonist for the treatment of acute attacks of hereditary angioedema (HAE). Priority Designation was granted on December 20, 2007 and the PDUFA goal date for the application was determined to be April 26, 2008. An Advisory Committee (AC) meeting was scheduled for February 20, 2008, but was cancelled. Jerini was informed of this decision by telephone on January 2, 2008. On January 8, 2008, a Bloomberg press release announced the cancellation of the AC meeting and implied that this removed one obstacle to approval. The Agency was concerned that the interpretation of the press release may cause public misconception as to the outcome of the Agency's review of the application. On January 11, 2008, a teleconference was held with Jerini to convey the intent of the cancellation of the AC meeting.

On February 15, 2008, Jerini requested a 90-day conference to discuss the progress of the review and to learn of any potential new observations made during the review to date and what could be done to address potential concerns regarding approvability. In the request, Jerini mentioned that additional efficacy data obtained from the open-label extensions to Phase 3 studies together with new data and statistical efficacy analyses of both Phase 3 studies would be submitted to the NDA. The additional efficacy data was submitted on February 18, 2008 and again in the briefing document on February 27, 2008. Jerini requested to discuss whether the information would be allowed in the current review cycle and if so, would the Agency extend the time of the review cycle.

2.0 DISCUSSION

Jerini began the discussion with a slide presentation of the efficacy data for two Phase 3 trials FAST-1 and FAST-2. Jerini stated that the two studies were identical in design and protocol with the exception of the inclusion of tranexamic acid (TA) in FAST-2 and placebo in FAST-1. The primary endpoint was time to onset of symptom relief and the secondary endpoints included response rate for symptom relief at 4 hours and time to "almost complete symptom relief". The results for icatibant are consistent for median time to onset of symptom relief in both studies. The difference is that in FAST-1 statistical significance was not achieved. Jerini noted that there is a greater predominance in FAST-1 of subjects with abdominal pain and time to relief of abdominal pain is short in both studies possibly attributable to an analgesic placebo effect. Jerini stated that icatibant's consistent performance is confirmed in the data contained in the NDA and the most recent efficacy amendment, which includes additional efficacy and safety information from the open-label extensions. Median time to symptom relief in the abdominal and cutaneous attacks is approximately two hours. The efficacy of icatibant is the same in treatment for additional attacks. In 61 laryngeal attacks, time to regression of symptoms is approximately one hour. To place the data in regulatory perspective Jerini stated that in one study there is no statistical significance. If approval is based on one study plus confirmatory evidence then FAST-2 would be the pivotal study. If FAST-1 is considered confirmatory then the open label data would support the FAST-1 study. The February 18, 2008 amendment contains open label data from last spring that supports the

FAST-1 study. Jerini inquired how the additional information submitted would be handled by the Agency.

The Agency responded that the additional information will be considered, but asked if Jerini has any new data that would support the efficacy of TA in HAE. The Agency raised the question about the efficacy of the active comparator, TA. Jerini stated that a superiority study does not have to prove that the comparator is effective as long as the comparator does not perform worse than placebo. The Agency noted that one could look at the data and conclude that TA is worse than placebo. The Agency inquired if Jerini had any additional information about the efficacy of TA for the treatment of acute attacks of HAE. Jerini agreed that it has not been proven that the active comparator works for the treatment of acute attacks of HAE and does not have any additional information regarding TA to submit. The Agency stated it will consider the information Jerini provided and determine how to handle the additional open-label information. The Agency inquired if Jerini had thought about any further clinical studies with icatibant. Jerini indicated that they have not thought about additional clinical studies.

The Agency inquired as to why the verbal descriptor scale (VDS) was not included in the Phase 3 studies. In Study 4102, the VDS was described as the gold standard when compared to the visual analog scale (VAS) instrument. Jerini responded that the design of the Phase 3 studies limited the number of assessments to be tested. Jerini also asked if the Agency considered VDS as an appropriate instrument. The Agency stated that if the VDS is the gold standard, for future studies the instrument should be included. In addition, the Agency noted that since the injection causes significant irritation, precautions should be taken to maintain blinding in the study. Jerini noted that based upon an Agency recommendation, they made the definition of responder more stringent to account for any blinding issues.

3.0 ATTACHMENTS

Slide presentation and bulleted points for the presentation.

FAST 1&2 Studies
Main Efficacy Endpoints

	FAST-2			FAST-1		
	Icatibant	TA	p value	Icatibant	Placebo	p value
No. patients in ITT Population	36	38		27	29	
Median time to onset of symptom relief (h)	2.0	12.0	< 0.001	2.5	4.6	0.142
Response rate at 4 hours after start of treatment (%)	80.0	30.6	≤ 0.001	66.7	46.4	0.176
Median time to almost complete symptom relief for all symptoms (h)	10.0	51.0	≤ 0.001	8.5	23.3	0.069

Jerini

Time to Onset of Symptom Relief (Hours)

	FAST 2			FAST 1		
Efficacy endpoint	Icatibant	TA	p value	Icatibant	Placebo	p value
Cutaneous swelling	2.6	18.1	<0.001	3.1	10.2	0.039
Cutaneous pain	1.5	12.0	0.003	1.6	9.0	0.007
Abdominal pain	1.6	3.5	0.026	2.0	3.3	0.056

Jerini

Open Label Confirmatory Data

- >500 abdominal & cutaneous attacks:
  time of onset of symptom relief – median of about 2 hours
- 61 laryngeal attacks:
  time to regression of symptoms – median of about 1 hour

Jerini

Jerini AG Presentation
NDA 22-150, 90 Day Meeting
March 5, 2008

1. Efficacy of icatibant assessed in 2 phase III trials: FAST-2 and FAST-1 – both to assess symptomatic relief in acute attacks of Hereditary Angioedema

2. These 2 studies had identical designs and identical protocols except comparator: TA in FAST-2, placebo in FAST-1

3. Primary endpoint was time to onset of symptom relief

4. Key secondary endpoints include response rate for symptom relief at 4 hours and time to "almost complete symptom relief"

5. Just quickly: In FAST-2 these are the results for the primary endpoint and for the key secondary endpoints

6. Here are the results for FAST-1 – slide 1

7. Overall, the results are consistent: Icatibant performed the same in both studies. But in FAST-1, statistical significance was not achieved.

8. What accounts for the lack of statistical significance of FAST-1?

9. The first is the greater predominance in FAST-1 of subjects whose most significant symptom was abdominal pain – around 50% in FAST-1 and around 35% in FAST-2 – slide - In both FAST-2 and FAST-1, time to relief of abdominal pain in the control arms was rather short in comparison to the other symptoms – in all likelihood a classic analgesic placebo effect in a pain study.

10. The placebo effect in the control arm, the higher percentage of abdominal pain as the index symptom in FAST-1, and – second - the smaller number of patients in FAST-1 combined to undermine the ability of the study to reach statistical significance. But as you can see, icatibant performed the same in both studies for the main symptoms, abdominal pain, cutaneous swelling and cutaneous pain.

11. The OL data (both in NDA and updated in the recent efficacy amendment) confirm icatibant's performance. There were more than 100 subjects and more than 500 HAE attacks in the OL studies.

    - The time to symptom relief in the abdominal and cutaneous attacks was about 2 hours
    - Efficacy of icatibant the same when patients were treated for additional attacks
    - In 61 laryngeal attacks: time to regression of symptoms was about 1 hour

12. The open label data confirm the performance of icatibant in FAST-2 and FAST-1 – the drug provides symptomatic relief in a median of about 2 hours in abdominal and cutaneous attacks. The OL data also show efficacy of icatibant in laryngeal attacks - time to regression of symptoms was about 1 hour

13. The data demonstrate the efficacy of icatibant in treatment of acute attacks of HAE.

Drafted by: chill/March 15, 2008

Initialed by: Seymour/March 20, 2008

Li/March 20, 2008

Chowdhury/March 24, 2008

Finalized by: chill/March 24, 2008

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/s/

Carol F. Hill
3/24/2008 06:17:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-150

Jerini US Inc.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, PharmD
Authorized U.S. Agent

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Firazyr 30 mg [redacted] (b) (4)

We also refer to your February 20, 2008, correspondence, received February 20, 2008, requesting a meeting to discuss the progress of the review and to gain knowledge of any potential concerns and what can be done to address these regarding approvability.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: March 5, 2008
Time: 4 pm to 5 pm
Location: Food and Drug Administration
Center for Drug Evaluation and Research
White Oak, Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Participants (tentative):

Office of Drug Evaluation II
Curtis Rosebraugh, MD, Acting Director

Division of Pulmonary and Allergy Participants
Badrul A. Chowdhury, M.D., Ph.D., Director
Sally Seymour, M.D., Acting Deputy Director/Team Leader
Anthony Durmowicz, M.D., Clinical Reviewer
Timothy McGovern, Ph.D., Pharmacology/Toxicology Supervisor
Molly Shea, Ph.D., Pharmacology/Toxicology Reviewer

Division of Pre-Marketing Assessment I
Ali Al-Hakim, Ph.D., Chief, Branch II
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead
Eugenia M. Nashed, Ph.D., CMC Reviewer

Division of Clinical Pharmacology
Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader
Partha Roy, Ph.D., Clinical Pharmacology Reviewer
Nitin Mehrotra, Ph.D., Visiting Associate
Yaning Wang, Ph.D., Visiting Scientist

Division of Biometrics II
Qian H. Li, Sc.D., Statistical Team Leader

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at carol.hill@fda.hhs.gov so the security staff may have time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Carol Hill, extension 61226; the division secretary, extension 62300.

As previously discussed, the background information for this meeting (three copies to the NDA and 20 desk copies to me) will be provided on February 25, 2008. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by February 26, 2008, we may cancel or reschedule the meeting.

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Hill, M.S.
Regulatory Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Carol F. Hill
2/26/2008 08:06:22 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **February 14, 2008**

To: **Glen Park, PharmD** **Authorized US Agent**	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: **Jerini US, Inc**	Division of Pulmonary and Allergy Products
Fax number: 212-681-2105	**Fax number:** 301-796-9728
Phone number: 212-681-2100	**Phone number:** 301-796-1226

Subject: **NDA 22-150 – Clinical Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-150
Jerini US, Inc.
Firazyr

We are in the process of reviewing your application and have the following requests for information to assist in our assessment of your application. Please forward this information as soon as possible.

1. Provide the study number and patient ID for each of the 5 cases of urticaria reported for icatibant in the Integrated Summary of Safety (ISS).

2. Summarize vital signs by treatment group (icatibant, placebo, tranexamic acid). Specify any outliers and shifts from normal to abnormal.

3. Provide the criteria used for categorizing laboratory parameters as normal/abnormal or as adverse events in the Phase 3 studies.

If you have any questions, contact Carol Hill, Regulatory Project Manager at 301-796-1226.

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/s/

Carol F. Hill
2/14/2008 01:32:21 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **January 31, 2008**

To: **Glen D. Park, PharmD** **Authorized US Agent**	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: **Jerini US Inc.** **c/o Target Health**	Division of Pulmonary and Allergy Products
Fax number: 212-681-2105	**Fax number:** 301-796-9728
Phone number: 212-681-2100	**Phone number:** 301-796-1226

Subject: **NDA 22-150 –Clinical Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-150
Jerini US Inc.
Firazyr (icatibant)

We are in the process of reviewing your application and have the following requests for information to assist in our assessment of your application. The outcome of the action to be taken for this application is contingent upon timely receipt of this information during the review cycle. Please forward this information as soon as possible.

1. Provide a copy of the EU-approved product label for tranexamic acid, the active comparator used in Study 2102.

2. As a follow-up to our January 8, 2008, 74-day letter, provide the definitions for the following abbreviations used in the Patient Data Listings (Section 17.2) in the JE049 #2103 Clinical Study Report: NA, ND, NK, and UNK.

If you have any questions, contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

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/s/

Carol F. Hill
1/31/2008 01:28:02 PM
CSO

MEMORANDUM

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

DATE: January 31, 2008

TO: Glen Park, Pharm. D., Jerini US, Inc.

FROM: Carol Hill, Regulatory Project Manager, DPAP

SUBJECT: **Summary of January 25, 2008 Teleconference**
NDA 22-150, Firazyr (icatibant acetate)

The teleconference held on January 25, 2008 was requested by Qian Li, Sc. D., Statistical Team Leader and statistical reviewer for NDA 22-150. The teleconference was scheduled to discuss information included in the Visual Analogue Scale (VAS) assessment dataset, local tolerability and rescue medication datasets. Jerini was asked to explain the organization of the data so that the information assessed during the double-blind treatment can be identified. The following list of requests was emailed to Jerini on January 31, 2008 after the teleconference.

1. Describe how to identify the VAS assessments for the first attack during the double-blind treatment period from the VAS dataset (SDVAS).

2. Explain why there are duplicate records for a patient's attack for one symptom at one assessment time point. See attached list from SAS output below.

3. Describe how to identify the local tolerability assessment for the first attack during the double-blind treatment period from the dataset, ASSESS.

4. Describe how to identify the rescue medication used for the first attack during the double-blind treatment period from dataset, CONMED.

Attachment

dup.lst (33 KB)

Jerini US, Inc. Attendees

Glen Park, Pharm. D., US Regulatory Affairs
Brigitte Hoch, Project Management
Bernd Rosenkranz, Clinical Development
Mike Bowden, Clinical Advisor
Brita Kulke, Regulatory Associate
Guenter Schultz, Head of Regulatory
Jochen Knolle, CSO

(b) (4)

drafted: chill/January 30, 2008
initialed: li/January 30, 2008
finalized: chill/January 31, 2008

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/s/

Carol F. Hill
1/31/2008 01:26:49 PM
CSO

-DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**
TO *(Division/Office)*: PharmTox Review Team (Drs. Molly Shea and Tim McGovern)		FROM: Prasad Peri, Ph.D. PAL for DPAP in ONDQA/DPA1/Branch 2	
DATE Jan 23, 2008	NDA. 22-150	TYPE OF DOCUMENT: NDA (Priority)	DATE OF DOCUMENT 26-Oct-2008
NAME OF DRUG Firazyr Injection	PRIORITY CONSIDERATION: P	CLASSIFICATION OF DRUG: 1	DESIRED COMPLETION DATE Sept 30, 2007
NAME OF FIRM: Jerini Inc.			

REASON FOR REQUEST: Evaluation of

Please evaluate the proposed levels of impurities proposed in the drug substance and drug product specifications for safety under the paradigm of the recommendations made during the TIDES Conference (see below). In addition, **The qualifications studies presented in section 3.2.S.3.2.3.3, -4.2, and -4.3 (Bridging Toxicology) need to be evaluated by the PharmTox Team**. Note the Agency agreed to the limits proposed at the "TIDES Conference 2005" for proteins and peptides. NDA is all electronic.

COMMENTS/SPECIAL INSTRUCTIONS: See below.

Product specific leachables studies demonstrated low and acceptable levels of leachables with this container closure system, when on contact with the drug product formulation. These studies are discussed in Section 3.2.P.2.4.
Compatibility of the formulation with the proposed container closure system is demonstrated through ongoing stability studies. The stability results for migration products and degradants are provided in Section 3.2.P.8.1 and Section 3.2.P.8.3.

Several degradation products have been identified and specified. Various unidentified impurities are also specified by their relative retention times. It is noted that [redacted] (b) (4) (a known metabolite) were synthesized and fully characterized and used in the drug substance stability programs. Note that the largest unidentified impurities [redacted] (b) (4) have greater than the identification threshold and no data on these are provided in samples that are stored at 25°C. The sponsor was asked to provide identifications of these impurities in the 74 day letters. In addition the levels of proposed leachables need to be evaluated.

Leachable profiles for [redacted] (b) (4) syringe components [redacted] (b) (4) and two alternate plunger stopper formulations [redacted] (b) (4) were assessed by [redacted] (b) (4) in comparison with storage in glass ampoules. A sterile 10 mg/mL icatibant formulation identical to the formulation proposed for marketing was studied. Based on these studies the [redacted] (b) (4) stopper was preferred. Note that the leachables studies were performed on [redacted] (b) (4). The difference

should be considered during evaluation and leachables data in the to-be marketed drug product will need to be requested.

Leachables termed as "Migration product were found (b) (4) by HPLC. An increase in the contents of the migration products was not observed under any of the storage conditions studied. The content of (b) (4) (b) (4) changed from the 'not detected' (LOD (b) (4) to a detectable but negligible quantity (e.g. (b) (4) observed in batches 06261JR and 06271JR) after 6 months storage at 40°C / 75% RH.
Otherwise, thus under the recommended storage conditions, there is no evidence that the potential migration products (b) (4) leach into the formulation and so they do not contribute to the sum of all the degradation products, see data provided in Attachment 2.

The applicant needs to address the identity of these impurities at the earliest. Note that the threshold for "minimal identification (b) (4) "fully identified and characterized (b) (4)" and "fully identified, characterized and qualification (b) (4) are considered the regulatory for peptides and these were publicly announced in the TIDES conference 2005, by Dr. Blair Fraser. The sponsor indicates that the drug product degradants and impurities that are above the threshold for identification are being characterized and their limits are set to (b) (4). The limit of total degradants is set at (b) (4). It is noted that none of the unidentified impurities are above the (b) (4) limit.

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

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 /s/
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Ali Al-Hakim
1/23/2008 05:24:25 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: January 23, 2008

To: Glen D. Park, PharmD Authorized US Agent	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: Jerini US Inc. c/o Target Health	Division of Pulmonary and Allergy Products
Fax number: 212-681-2105	**Fax number:** 301-796-9728
Phone number: 212-681-2100	**Phone number:** 301-796-1226

Subject: NDA 22-150 –January 11, 2008 Tcon Minutes

Total no. of pages including cover: 4

Comments: Please acknowledge receipt.

Document to be mailed: ☐ YES ☑ NO

MEMORANDUM OF TELECONFERENCE

APPLICATION: NDA 22-150
SPONSOR: Jerini US, Inc.
DRUG NAME: Firazyr
DATE: January 11, 2008

Jerini's Representatives:
Jens Schneider-Mergener, CEO
Jochen Knolle, Chief Scientific Officer
Bernd Rosenkranz, Head of Clinical Development
(b) (4)
Guenter Schultz, Regulatory Affairs
Glen Park, Target Health Inc., US Regulatory Agent

Division of Pulmonary & Allergy Products Representatives:
Curtis Rosebraugh, M.D., Ph.D., Acting Director of Office of New Drugs
Leah Ripper, Associate Director for Regulatory Affairs, Office of Drug Evaluation II
Badrul Chowdhury, M.D., Ph.D., Division Director
Anthony Durmowicz, M.D., Ph.D., Clinical Reviewer
Carol Hill, MS, Regulatory Project Manager

BACKGROUND:
Jerini US, Inc. submitted a New Drug Application (NDA) dated October 22, 2007, received October 26, 2007 for icatibant (Firazyr), a bradykinin type-2 receptor antagonist for the treatment of acute attacks of hereditary angioedema (AE). An Advisory Committee (AC) meeting was scheduled to take place on February 20, 2008, but was cancelled. Jerini was informed of this decision by telephone on January 2, 2008 and expressed during the call that this may not be good news for their potential approval. On January 8, 2008 a Bloomberg press release announced the cancellation of the AC meeting thus, "removing one obstacle to approval" of icatibant. This was the same day that Jerini confirmed receipt of the 74 day letter from the Agency.

Discussion:
In light of a recent Bloomberg press release concerning Jerini's icatibant product, the Agency requested on January 11, 2008, a teleconference with Jerini to convey the intent of cancellation of an AC meeting to avoid any misconceptions. The Agency expressed concern that the Bloomberg article was misleading in stating that the cancellation of the February 20, 2008 AC meeting removed one obstacle to approval. The Agency explained that cancellations of AC meetings can occur for several reasons. For example, an AC meeting can be canceled when a preliminary review of an application reveals an overwhelming evidence of efficacy, no safety concerns, and the drug is of an already well characterized class. An AC meeting may also be canceled if a drug has not demonstrated safety and /or efficacy, and the Agency has determined that having an AC meeting in such a situation would not be worthwhile use of resource and time.

The Agency pointed out that Jerini's situation falls in the latter category. It was noted that the review issues regarding efficacy were discussed at the January 24, 2007, Pre-NDA meeting and again in the 74 day letter.

The Agency further explained that experience has shown that potential legal ramifications could occur to the sponsor if investors felt mislead by such a comment. The Agency informed the sponsor that we were not making accusations, but wanted to make Jerini aware of an erroneous press statement and to clarify the reasons for which an AC meeting may be canceled. The Agency also said that we felt we should draw their attention to press statements of this type, as we became aware of them, so that they would have the opportunity to correct any misperceptions that may be created by an erroneous press report. Jerini confirmed that the Agency's comments and advice were fully understood and were grateful that this issue was brought to their attention.

Drafted: chill/January 22, 2008
Initialed: Durmowicz/January 22, 2008
Rosebraugh/January 22, 2008
Chowdhury/January 22, 2008
Finalized: chill/January 23, 2008

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/s/

Carol F. Hill
1/23/2008 01:39:20 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-150

Jerini US Inc.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, PharmD
Authorized U.S. Agent

Dear Dr. Park:

Please refer to your new drug application (NDA) dated October 22, 2007, received October 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Firazyr 30 mg (b) (4)

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application on December 25, 2007. The review classification for this application is Priority. Therefore, the user fee goal date is April 26, 2008. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 12, 2008.

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

1. As discussed in the January 24, 2007, Pre-NDA meeting, you do not have two confirmatory studies demonstrating the efficacy of icatibant for the proposed indication. Of the two Phase 3 studies included in your NDA submission, Study 2102 used an active comparator which is not approved for the treatment of HAE in the United States, and Study 2103 did not demonstrate a statistically significant benefit of icatibant over placebo

for the primary efficacy endpoint, time to onset of symptom relief. The adequacy of your data to support the efficacy of icatibant for the proposed indication will be a review issue.

2. The proposed indication, treatment of hereditary angioedema, is broad and does not reflect your clinical development program. The efficacy and safety studies conducted in support of this application addressed the treatment of acute attacks of HAE specifically, not a general treatment indication.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information.

3. Define the following abbreviations used in the Patient Data Listings (Section 17.2) in the JE049 #2103 Clinical Study Report: NA, ND, NK, and UNK.

4. Provide the median time to onset of symptom relief for laryngeal attack patients in Studies 2102 and 2103.

5. Provide samples of the drug product for our review.

6. Provide the identity of all impurities that appear at or above (b) (4) concentration of the drug substance. All impurities above the threshold of (b) (4) should be identified and well characterized.

7. We note that the leachables data you have provided used a (b) (4) as opposed to the 3 mL syringe which is proposed for the commercial distribution. Provide extractables and leachables data from the commercial container closure system or demonstrate with adequate data that the submitted results are representative of the expected levels of leachables in the drug product stored up to the shelf life in the proposed container closure. Note that adequate toxicological assessment will be needed for these leachables.

8. The completion of nonclinical chronic repeat dose toxicity studies (6-month in rat and 9-month in dog) via the subcutaneous route of administration is required to support chronic intermittent clinical dosing. The icatibant labeling will reflect a clinical dosing regimen that is supported by the nonclinical toxicology studies in both dose and duration. At this time you have nonclinical support for subcutaneous clinical dosing for up to 13-weeks duration. Provide the current status of your chronic repeat dose studies in the rat and the dog and the status of your carcinogenicity studies, which were requested at the Pre-NDA meeting.

9. As relayed to you at the Pre-NDA meeting, qualify any impurity and/or degradant that exceeds the qualification threshold of (b) (4) for peptides.

10. Please submit the following information in support of the population PK/PD analysis in study report JE049-5108.

    a. Provide datasets used for model development and validation as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

    b. Model codes or control streams and output listings should be provided for all major model building steps. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

    c. Provide a model development decision tree and /or table which gives an overview of modeling steps.

We have the following labeling comments regarding conformance of your proposed labeling with the Physician Labeling Rule (PLR) format requirements.

General Comments

11. For specific requirements on the content and format of labeling for human prescription drug and biologic products refer to 21 CFR 201.57. Also see Draft Guidance for Industry: Labeling for Human Prescription Drug and Biologic Products – Implementing the New Content and Format Requirements (Implementation Guidance).

12. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling format.

Highlights

13. In the DOSAGE AND ADMINISTRATION section, include critical differences among population subsets; monitoring recommendations, and other clinically significant clinical pharmacologic information that affects dosing recommendations if applicable.

14. Also in the DOSAGE AND ADMINISTRATION section, major limitations for use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. [See 21 CFR 201.57(a)(6)]

15. In the CONTRAINDICATIONS section, the summarized labeling information does not match the cited references. (b) (4)

16. The drug name should be followed by the drug's dosage form and route of administration. [See 21 CFR 201.57(a)(2)] (b) (4)

17. In the ADVERSE REACTIONS section, provide the manufacturer's phone number for reporting suspected adverse reaction or provide the web address of the direct link to the site for voluntary reporting of adverse reactions. An email address or general link to a company's website cannot be used to meet the requirement to have adverse reactions reporting contact information. [See 21 CFR 201.57(a)(11)]

18. A horizontal line must separate the Highlights and FPI:C. [See 21 CFR 201.57(d)(2)]

Full Prescribing Information: Contents

19. The table of contents should be limited in length to one-half page.

20. The format and wording of the section and subsection headings used in the table of contents must match the section and subsection headings used in the FPI. [See 21 CFR 201.57(b)] Subsections of sections 2, 4, 5, 8, and 12 in the table of contents do not match those listed in the FPI.

21. When the section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed." (b) (4)

Full Prescribing Information:

22. See comments 20 and 21.

23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Warnings and Precautions (5.3)* not (*see section 5.3*). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance] Also ensure that the section referenced is listed in the FPI.

24. In the section CONTRAINDICATIONS, (b) (4) is omitted. Also the subsection title does not match the same subsection number in the FPI:C. See comment 10 and arrange the subsections so that they match those in the FPI:C.

25. Include the manufacturer information at the end of the labeling.

In addition, we have the following comment regarding the carton and container labels.

26. Remove [redacted] (b) (4) next to the proprietary name as it detracts from the propriety name (21 CFR 201.15 (a)(6)) and decreases the relative prominence of the established name (21 CFR 201.10(g)(2)).

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

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
1/8/2008 11:07:10 AM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: James McVey, Team Leader
Office of Pharmaceutical Science
New Drug Microbiology Staff

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Pulmonary and Allergy Products
Carol Hill, RPM, 301-796-1226

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/21/07		22-126	N	10-22-07

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Firazyr (icatibant)	Yes	Bradykinin receptor B2 antagonist	March 7, 2008

NAME OF FIRM: Jerini US Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate the following: proposed microbial limits, endotoxins limits and information concerning the validation of the sterilzation cycle presented in Section 3.2.P.3.5. Note that this is a [redacted] (b) (4) This is an eCTD submission and can be reviewed in the EDR.

SIGNATURE OF REQUESTOR
Carol Hill

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Carol F. Hill
12/20/2007 05:07:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-150

PRIORITY REVIEW DESIGNATION

Jerini US Inc.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen K. Park, Pharm. D.
Authorized U.S. Agent

Dear Dr. Park:

Please refer to your new drug application (NDA) dated, October 22, 2007, received October 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Firazyr (icatibant) 30 mg [redacted] (b) (4).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is April 26, 2008.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before January 8, 2008.

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
12/20/2007 11:07:21 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **December 12, 2007**

To: **Glen D. Park, PharmD** **Authorized US Agent**	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: **Jerini US Inc.** **c/o Target Health**	Division of Pulmonary and Allergy Products
Fax number: 212-681-2105	**Fax number:** 301-796-9728
Phone number: 212-681-2100	**Phone number:** 301-796-1226

Subject: **NDA 22-150 – Clinical Information Request**

Total no. of pages including cover: 3

Comments: Please acknowledge receipt.

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-150
Jerini US Inc.
Firazyr (icatibant)

We are in the process of reviewing your application and have the following requests for information to assist in our assessment of your application. The outcome of the action to be taken for this application is contingent upon timely receipt of this information during the review cycle. Please forward this information by December 28, 2007.

> We note that your Integrated Summary of Safety (ISS) is based on a pooled database of Phase 1, 2, and 3 studies, including both healthy volunteers and HAE patients. As discussed during the January 24, 2007, Pre-NDA meeting, we request that you submit your analysis and discussion with data pooled from the Phase 3 studies only, presenting the data from the controlled portion of the studies separately from the open-label portion. Phase 2 data should be analyzed and discussed separately in another section of the ISS.

If you have any questions, contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

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/s/

Carol F. Hill
12/12/2007 01:51:53 PM
CSO

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug, Marketing, Advertising and Communications (DDMAC) WO RM 1400

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Carol Hill, RPM 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 16, 2007		22-150	N	October 22, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Firzayr (icatibant acetate)	Priiority	Bradykinin receptor B2 antagonist	March 4, 2008

NAME OF FIRM: Jerini US, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Labeling Review. The NDA submission is entirely electronic. All review material may be found in EDR submission 10/22/07.
Link: \\CDSESUB1\EVSPROD\NDA022150\022150.ENX

SIGNATURE OF REQUESTOR
Carol Hill

METHOD OF DELIVERY (Check one)
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PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Carol F. Hill

11/16/2007 11:07:04 AM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Carol Hill, RPM, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 16, 2007		22-150	N	October 22, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Firazyr (icatibant acetate)	Priority	Bradykinin receptor B2 antagonist	March 4, 2008

NAME OF FIRM: Jerini US Inc.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Tradename review. The entire submission is electronic, all review material may be found in the EDR submission 10/22/07.
Link:\\CDSESUB1\EVSPROD\NDA022150\022150.ENX

PDUFA DATE: April 25, 2008
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA
HFD- /Division File
HFD- /RPM
HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER
Carol Hill

METHOD OF DELIVERY (Check one)
☒ DFS ONLY ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Carol F. Hill

11/16/2007 11:03:04 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-150

NDA ACKNOWLEDGMENT

Jerini US Inc.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, PharmD
Authorized U.S. Agent

Dear Dr. Park:

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

Name of Drug Product: Firazyr (icatibant acetate) Injection (b) (4) 30 mg

Date of Application: October 22, 2007

Date of Receipt: October 26, 2007

Our Reference Number: NDA 22-150

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 25, 2007 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

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

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

If you have any questions, call Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Carol F. Hill
11/6/2007 02:31:57 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)

DATE RECEIVED: 11/1/06 **DATE OF DOCUMENT:** 10/13/06	**DESIRED COMPLETION DATE:** 1/30/07	**OSE CONSULT #:** 2006-749

TO: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Products
HFD-570

THROUGH: Denise Toyer, Pharm D, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Richard Abate, RPh, MS, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Firazyr** (Icatibant Acetate) Injection 30 mg/3 mL pre-filled syringe **IND#:** 68,214	**IND SPONSOR:** Jerini US, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Firazyr. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends that labels and labeling be submitted for review and comment as soon as they are available. We would like to evaluate the delivery device to determine if the device or its labeling can lead to medication errors.

3. DDMAC finds the proprietary name, Firazyr, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Nancy Clark, project managers, at 301-796-1187.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 12/18/2006

IND #: 68,214

NAME OF DRUG: **Firazyr**
(Icatibant Acetate) Injection
30 mg/3 mL Pre-filled Syringe

IND HOLDER: Jerini US, Inc

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Products (HFD-570), for assessment of the proprietary name, "Firazyr," regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were not provided for review and comment.

PRODUCT INFORMATION

Firazyr (Icatibant Acetate) is an investigational new drug being developed for the treatment of hereditary angioedema. Firazyr will be administered as a subcutaneous injection as a single dose of 30 mg. Firazyr will be supplied as a pre-filled syringe containing 30 mg/3 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Firazyr to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] WWW location http://www.uspto.gov/tmdb/index html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written requisitions and one verbal requisition study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a product must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Firazyr. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Firazyr, acceptable from a promotional perspective.

2. The Expert Panel identified twenty-two proprietary names that were thought to have the potential for confusion with Firazyr. Of these twenty-two names, sixteen were not reviewed further due to lack of significant look-alike and/or sound-alike similarities to Firazyr, in addition to differentiating product characteristics that may include, indication for use, product strength, usual dose, route of administration, frequency of administration, dosage form, prescribing population, patient population, storage conditions, product unavailability and/or area of marketing or distribution. The names not further reviewed include the following: Fergon, Fioricet, Fiorinal, Fortaz, Furaspor, Peroxyl, TearGard, Terazol, Tinamar, Tikosyn, Vesicare, Viracept, Virazole, (b) (4), Ziravir (Italy), and Ziradryl. The remaining names reviewed are listed in table 1 (See below) along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Firazyr	Icatibant Acetate Injection: 30 mg/3 mL	30 mg subcutaneously one time.	
FeraSul	Ferrous Sulfate Tablet: 325 mg	1 tablet orally twice to three times daily.	SA
Flagyl	Metronidazole Tablet: 250 mg and 500 mg Capsule: 375 mg Powder for Injection: 500 mg	1 tablet orally three times daily.	LA
Pherazine (discontinued)	Promethazine in combination with Dextromethorphan HBr (DM) or Phenylephrine (VC) and/or Codeine Sulfate. Syrup: 6.25 mg/5 mL	1 teaspoonful every four to six hours as needed for cough.	SA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Firazyr	Icatibant Acetate Injection: 30 mg/3 mL	30 mg subcutaneously one time.	
Tiazac	Diltiazem Hydrochloride Extended-release Capsule: 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg	1 capsule by mouth daily.	LA
Trizivir	Abacavir/Lamivudine/Zidovudine Tablet: 300 mg/150 mg/300 mg	One tablet by mouth twice daily.	LA
Verazinc	Zinc Sulfate Capsule: 220 mg	One capsule by mouth daily.	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Firazyr with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two pharmacy requisition orders were written, each consisting of a combination of marketed and unapproved drug products and an order for Firazyr (see below). These orders were optically scanned and one order was delivered to a random sample of the participating health professionals via e-mail. In addition, one of the requisition orders was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal requisition orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient Requisition order #1: Firazyr 30 mg	Firazyr 30 mg # 5
Inpatient Requisition order #2: Firazyr 30mg	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Firazyr, DMETS identified names with similar appearance and sound to Firazyr. The primary concerns relating to look-alike and sound-alike confusion with Firazyr are FeraSul, Flagyl, Pherazine, Tiazac, Trizivir, and Verazinc. Additionally, we evaluated the proposed package of a pre-filled syringe and identified concerns of potential medication error from route of administration and improper dose.

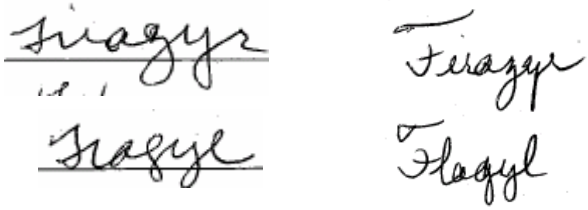
DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Firazyr.

1. Sound-Alike and/or Look-Alike Concerns

DMETS has the following comments concerning the names that were identified as potentially sounding and looking similar to Firazyr.

a. Flagyl was identified as having look-alike characteristics with the proposed name, Firazyr. Flagyl (Metronidazole) is an antibiotic indicated for amebiasis and infections caused by anaerobic bacteria. The usual dose of Flagyl is 250 mg to 500 mg three times daily.

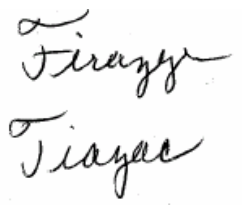
Flagyl looks similar to Firazyr. Both names start with the letter “F” followed by an “i” in Firazyr or an “l” in Flagyl. The “i” and “l” appear similar when scripted. In addition, the letter combination of “azy” in Firazyr looks similar to the combination “agy” in Flagyl due to the downstroke of “z” and “g.” However, Firazyr contains an additional letter “r” between the “i” and “a” which provides added length to this name compared to Flagyl. The final letters, “r” in Firazir compared to the “l” in Flagyl, also provide orthographic differentiation.

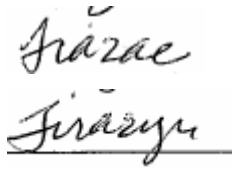


While Flagyl and Firazyr are prescription medications with the same numerical dose (30 mg or **one** pre-filled syringe vs. **one** tablet), dosage form (injection), and similar route of administration, (**subcutaneous** vs. **intravenous** and oral), these products have multiple differing characteristics. These differences include the following: strength (30 mg/3 mL vs. 250 mg. 375 mg, and 500 mg), frequency of administration (one time vs. three times daily to every six hours), and indication for use (hereditary angioedema vs. infection). In addition, Firazyr is indicated for a specific patient population who have hereditary angioedema which will limit its use. While Flagyl and Firazyr have look-alike similarities, we believe that the differing product characteristics minimize the potential for confusion.

b. Tiazac was identified as having look-alike characteristics with the proposed name, Firazyr. Tiazac (Diltiazem hydrochloride) is indicated for hypertension and chronic stable angina. The usual dose of Tiazac is one capsule (120 mg to 360 mg) daily.

Tiazac looks similar to Firazyr. This stems from beginning letter combination of each name, “Firaz” in Firazyr compared to “Tiaz” in Tiazac, which look similar when scripted. However, Firazyr contains an “r” between the “i” and “a” which provides added length to this name compared to Tiazac. The endings, “yr” in Firazyr compared to “ac” in Tiazac, also provide orthographic differentiation.

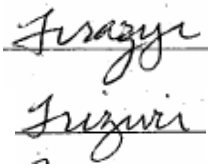




While Tiazac and Firazyr share dose (30 mg or **one** syringe vs. **one** capsule) and a similar numeric strength (**30** mg/3 mL vs. **300** mg), these products have multiple differing characteristics. These differences include dosage form (injection vs. capsule), route of administration (subcutaneous vs. oral), frequency of use (one time vs. daily), duration of therapy (single dose vs. chronically), and indication of use (hereditary angioedema vs. hypertension). Additionally, Tiazac is available in multiple strengths requiring the strength to be specified on a prescription order. While the names share some orthographic similarity, the multiple differing product characteristics between Tiazac and Firazyr minimize the potential for confusion between these products.

c. Trizivir was identified as having look-alike characteristics with the proposed name, Firazyr. Trizivir (Abacavir//Lamivudine/Zidovudine) is indicated for human immunodeficiency virus infection. The usual dose of Trizivir is one tablet twice daily.

Trizivir looks similar to Firazyr. The look-alike similarities stem from the beginning letter combinations “Firaz” in Firazyr which looks similar to “Triz” in Trizivir when scripted. In addition, both names end in “r.” However, the downstroke of the “y” in Firazyr compared to letter combination “ivi” in Trizivir provides orthographic differentiation.



While Firazyr and Trizivir share the characteristics of dose (30 mg or **one** syringe vs. **one** tablet) and each is available in a single strength (30 mg/3 mL vs. 300 mg/150 mg/300 mg), they have multiple differing product characteristics. These differences include dosage form (injection vs. tablet), frequency of administration (one time vs. twice a day), route of administration (subcutaneous vs. oral), indication for use (hereditary angioedema vs. human immunodeficiency virus infection), and prescribing population (emergency room physicians or general practitioners vs. infectious disease specialists). Although Firazyr and Trizivir look similar, we believe the differing product characteristics minimize the potential for confusion between these products.

d. FeraSul was identified as having sound-alike characteristics with the proposed name, Firazyr. FeraSul (Ferrous Sulfate) is an over-the-counter medication indicated for iron deficiency. It is usually dosed at one tablet by mouth two or three times daily.

The sound-alike similarities are due to the almost identical beginning two syllables, “Fira” in Firazyr compared to “Fera” in FeraSul. The third syllable in each name begins with phonetically similar sounds, “z” in Firazyr compared to the “s” in FeraSul. However, the endings of “yr” in Firazyr compared to the “ul” in FeraSul provide some phonetic differentiation.

While Firazyr and FeraSul share a common dose (30 mg or **one** syringe vs. 325 mg or **one** tablet) and are each available in a single strength, these products share no other characteristics including strength (30 mg/3 mL vs. 325 mg), dosage form (injection vs. tablet), route of administration (subcutaneous vs. oral), frequency of administration (one time vs. two to three times daily), distribution (prescription vs. over-the-counter), and indication for use (hereditary angioedema vs. iron deficiency). In addition, prescribers usually order Ferrous Sulfate by the established name rather than the proprietary name. Therefore, although Firazyr and FeraSul sound similar, we believe the aforementioned product characteristics minimize the potential for confusion between these products.

e. Pherazine was identified as having sound-alike characteristics with the name, Firazyr. Pherazine (Promethazine HCl in combination with Dextromethorphan HBr or Phenylephrine HCl and Codeine Sulfate). The usual dose of Pherazine is one teaspoonful (5 mL) every four to six hours as needed.

Pherazine sounds similar to Firazyr. The sound-alike similarities stem from the first two syllables, “Fira” in Firazyr and “Phera” in Pherazine, having nearly identical pronunciation. However, the third syllable in each name, “zyr” in Firazyr comparied to “zine,” in Pherazine provide phonetic differentiation.

While Firazyr and Pherazine share an overlapping dose (30 mg or **one** syringe vs. 6.25 mg or 5 mL or **one** teaspoonful) and can be ordered in milliliters, they have many differing product characteristics. These differences include strength (30 mg/3 mL vs. 6.25 mg/5 mL), dosage form (injection vs. oral syrup), route of administration (subcutaneous vs. oral), frequency of administration (one time vs. every four to six hours), and indication for use (hereditary angioedema vs. cough suppressant). In addition, Pherazine has several combinations requiring a modifier (e.g., DM or VC) to be used in a prescription order. While Pherazine was removed from the market in 1995, many generic oral Promethazine combination products remain available. Thus, a prescription for Pherazine could be filled with a generic equivalent. However, DMETS believes the aforementioned differing product characteristics minimize the potential for these products to be confused.

f. Verazinc was identified as having sound-alike characteristics with Firazyr. Verazinc (Zinc Sulfate) is an over-the-counter supplement for zinc deficiency. The usual dose is 220 mg by mouth daily.

Verazinc sounds similar to Firazyr. The first two syllables, “Fira” in Firazyr compared to “Vera” are similar when spoken and rhyme. In addition, the last syllable in both names begin with the “zee” sound. However, the ending sounds, “zyr” in Firazyr compared to “zinc” in Verazinc, provide phonetic differentiation.

Other than numerical dose (30 mg or **one** syringe vs. 220 mg or **one** capsule), Firazyr and Verazinc do not share any overlapping product characteristics such as dosage form (injection vs. capsule), route of administration (subcutaneous vs. oral), product strength (30 mg/3 mL vs. 220 mg), dosing frequency (one dose vs. once daily), and distribution (prescription vs. over-the-counter). DMETS believes that the aforementioned product differences make it unlikely that Firazyr and Verazinc will be confused for one another.

2. Safety Concerns with the Pre-filled Syringe

DMETS notes the described 30 mg dose requires the administration of the entire contents of the pre-filled syringe. However, we question whether a pre-filled syringe will provide the appropriate dose for all patients. If during clinical trials the sponsor determines the dose varies based on weight or organ function, this pre-filled syringe may contribute to medication errors post approval. The inappropriate administration of the entire contents of the pre-filled syringe occurs frequently in post marketing surveillance of medications marketed in pre-filled syringes. In addition, incorrect route of administration has been reported in post marketing surveillance of pre-filled syringes. For example,the contents may be inadvertantly administered intravenously rather than the intended subcutaneous route based on the fact that practitioners may equate the prefilled syringe with giving the drug intravenously. Therefore, DMETS requests any medication errors identified during the clinical trials for Firazir be submitted at the time of the NDA review. We also request to review an actual model of the proposed device.

Appendix A: Prescription Study results for Firazyr

Inpatient Requisition 1	Inpatient Requisition 2	Verbal Requisition
Firazip	Firazyr	Ferzer
Tirazyr	firazyr	Verser
Firazip	Firazyr	Ferzier
Ferazip	Firazyr	Ferzer
Tirazip	Girazyr	Furzer
Terazyr	Firazyr	Ferzer
Ferazyr	Firazyr	Ferzir
Firazip	Firazyr	Furzir
Terazip	Firazyr	Fezer
Firazyn	Firazyr	
Firazrp	Zirazyr	
Firazip	Firazyr	
Ferazip	Firazyr	
Firazip	Firazyr	
Ferazep	Firazyr	
Terazip		
Tirazyr		
Firazip		
Tirazip		

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/s/

Richard Abate
5/9/2007 09:53:33 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/9/2007 01:36:05 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/9/2007 02:19:47 PM
DRUG SAFETY OFFICE REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: February 22, 2007

To: Claudia Julina Vice President, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: Jerini US, Inc.	Division of Pulmonary and Allergy Products
Fax number: 973-741-3100	**Fax number:** 301-796-9728
Phone number: 908-938-1192	**Phone number:** 301-796-1226

Subject: IND 68,214 – Meeting Minutes for January 24, 2007

Total no. of pages including cover: 51

Comments:

Document to be mailed: ☐ YES ☑ NO

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 24, 2007, 3:30 pm – 5:00 pm
Meeting Location:	FDA WO Bldg 22, Room 1417
Application Number:	IND 68,214
Product Name:	icatibant acetate
Received Briefing Package	December 21, 2006
Sponsor Name:	Jerini US, Inc.
Meeting Requestor:	Jerini US, Inc.
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder:	Carol Hill, M.S.
Meeting Attendees:	

Food and Drug Administration:

<u>Division of Pulmonary and Allergy Products</u>

Badrul A. Chowdhury, M.D., Ph.D., Division Director

Sally Seymour, M.D., Clinical Team Leader

Susan Limb, M.D., Clinical Reviewer

Timothy McGovern, Ph.D., Pharm/Tox Team Leader

Molly Shea, Ph.D., Pharm/Tox Reviewer

Joy Mele, M.S., Acting Statistical Team Leader

Ted Guo, Ph.D., Statistical Reviewer

Prasad Peri, Ph.D., PAL, ONDQA

Emmanuel Fadiran, R.Ph., Ph.D., Clin Pharm Team Leader

Sponsor Attendees:

(b) (4)

Laurence Jobron, Ph.D., Dir. Project Management, Jerini AG

Claudia Julina, M.S., VP Regulatory Affairs & QS, Jerini

Jochen Knolle, Ph.D., Chief Scientific Officer, Jerini AG

Andrea Ludwig, Pharm D., Dir. Pharmaceutical Development, Jerini AG

(b) (4)

Bernd Rosenkranz, M.D., FFPM, VP Clinical Development, Jerini AG

(b) (4)

Jens Schneider-Mergener, Ph.D., Prof., CEO, Jerini AG

(b) (4)

1.0 BACKGROUND

Jerini submitted a meeting request dated November 23, 2006, for a pre-NDA meeting to discuss the Division's recommendations for the best approach to the presentation and formatting of data in the marketing application and to ensure that Jerini's plan for electronic submission will adequately address the Division's requirements. A briefing package for this meeting was submitted on December 21, 2006. Upon review of the briefing package, the division responded to Jerini's questions via fax on January 19, 2007. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Jerini's questions are in **bold italics;** FDA's response is in *italics;* discussion is in normal font.

2.0 DISCUSSION

The purpose of this meeting is to further clarify and discuss the FDA responses to Jerini's questions which were faxed to Jerini on January 19, 2007. Jerini requested clarification of the following questions and additional comments contained in the fax: general question #1, additional CMC comment 2, non-clinical additional comments 1-3 and clinical questions #4, #5, and #7. Jerini agreed to all other FDA responses to questions and additional comments.

Jerini provided a slide presentation of an overview of icatibant's regulatory history and the clinical features of hereditary angioedema. See the attachments.

2.1 GENERAL

Question 1:

As previously agreed with the Agency (Meeting Minutes of Pre-NDA Meeting, March 1, 2005) Jerini will address pediatric studies after approval only. Therefore no pediatric studies will be submitted in the NDA.

Does the Agency Agree?

FDA Response to Question 1:

Your approach to establish efficacy and safety of icatibant in adults prior to conducting studies in pediatric subjects is reasonable. At the time of NDA submission, include your proposed pediatric development program.

Discussion:

Jerini proposed submission of the planned pediatric program for icatibant prior to NDA submission. The Division responded that Jerini may submit their pediatric plan prior to the NDA submission, but a review of the pediatric program prior to review of the NDA would not be guaranteed. The Division also noted that PREA is not applicable for orphan drugs.

2.2 CMC

Question 1:

Three registration batches of pre-filled syringes have been manufactured by the manufacturing facility intended for commercial supplies. Validation batches of the drug product in pre-filled syringes shall be manufactured after NDA submission. Jerini intends to submit the validation protocols for the drug product in the NDA and to submit the validation reports at a later stage.

Does the Agency agree?

FDA Response to Question1:

Your approach is reasonable. Note, however, that the sterility validation and sterility assurance of the manufacturing process in the NDA will be evaluated by microbiologists at CDER.

Inspectors from the Office of Compliance will evaluate the manufacturing sites. To expedite this process, have all sites ready for inspection at the time of NDA submission.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 2:

After change of manufacturer of the drug product, a primary stability program has been initiated. At the time of submission, 6-month primary stability data (3 batches) will be available. These data will be supported by 18-month stability data with an identical formulation and container closure system but generated by a different manufacturer. Jerini intends to file the 6-month primary stability data together with the supportive 18-month stability data.

The 9-month and 12-month datasets from the primary stability program will be submitted during the review period.

Does the agency agree?

FDA Response to Question 2:

Your approach is reasonable. Note, however, that the shelf life will be dependent on the stability data for the primary stability batches.

We encourage you to submit the additional stability datasets on or before the mid-cycle of the review period.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question3:

A description of the CMC program and a draft table of contents of the NDA are provided.

Does the Agency agree that the CMC data package described is sufficient for submission and filing of the NDA of icatibant acetate 10 mg/mL, solution for injection?

FDA Response to Question 3:

Your proposed format for the CMC technical portion of the application appears reasonable for filing.

Provide data for extractables and leachables from the container closure system. Update the drug product specifications as appropriate.

For ease of review of stability data, provide graphical representation of each attribute against time for individual and mean results.

Provide a sample of the drug product.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 4:

As this is an application for an orphan drug and the estimated concentration of icatibant acetate at the point of entry into the aquatic environment will be below 1 part per billion, Jerini proposes to claim a categorical exclusion from an environmental assessment as provided for in 21CFR25.31(b).

Does the Agency agree?

FDA Response to Question 4:

Although this is a review issue, your approach is reasonable.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Additional CMC Comments:

1. *For routine quality control of the elastomeric and plastic components, provide data for extractables and leachables from the container closure system at release and stability. Evaluate their levels for safety and update the drug product specifications as appropriate.*

2. *Provide comparative data for all unidentified impurities in the drug product for all batches manufactured so far. Identify all impurities to the*

extent possible. Consult ICH Q3A(R) and ICH Q3B(R) guidelines for general thresholds for qualification of impurities. The specific identification and qualification levels will be evaluated during the review period.

Discussion:

Jerini requested clarification regarding the guidelines and the Division's expectations for identification of and qualification of impurities of the drug product. Jerini stated that the guidelines for the threshold qualifications were inappropriate and asked if the recommendation should be the same as those presented at the Tides Conference of 2006. The Division confirmed that the thresholds for qualification and identification presented at the Tides 2006 Conference were in line with the Division's thinking.

3. *Provide Drug Master Files (DMFs) for all container closure systems in the NDA.*

4. *Submit English translations of three executed master batch records.*

2.3 NONCLINICAL

Question 1:

The proposed route of administration for icatibant in the treatment of HAE is by subcutaneous injection. In the development history of icatibant, to investigate its potential in other therapies, a number of nonclinical safety studies have been conducted via the inhaled and intranasal routes (summarized in Table 5.3-2, Appendix 5.3). Jerini has reviewed these studies and considers that, due to poor bioavailability via these routes (approximately 1% intranasally), they do not contribute to the evaluation of the safety of icatibant by subcutaneous injection. Jerini intends to briefly summarize the results in the overview and include these reports in Module 4, but does not intend to address the reports as part of the development program in the respective sections of the CTD.

Does the Agency agree?

FDA Response to Question 1:

We concur with your proposal.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Additional Nonclinical Comments:

1. *Although the proposed use of icatibant is for acute attacks of HAE, the actual anticipated use is considered chronic intermittent and patients may be exposed to icatibant for an extended part of their lives. Under this type of dosing scenario, additional nonclinical studies examining chronic exposure to icatibant are typically needed to support an NDA. These studies include:*

    a. *Chronic repeat dose toxicity studies in the rat (6 month) and the dog (9 month) via the clinical (subcutaneous) route of administration, and*

    b. *Two carcinogenicity studies to address the carcinogenic potential of icatibant.*

Discussion:
Jerini presented an overview of the nonclinical studies via a slide presentation (see attachment – Icatibant: Nonclinical, Additional comments). Jerini noted that dosing overages on a monthly basis compared to anticipated clinical use were built into the studies. The studies provided adequate dosing margins for clinical administrations of three 30 mg injections per day and no more than eight 30 mg injections per month.

Jerini asked that, given the nonclinical program, would additional studies be required for chronic intermittent treatment. The Division stated that chronic toxicity studies would be needed since the proposed use of the drug was considered a chronic intermittent exposure over a patient's life time. The Division typically assesses safety based on comparisons of animal and human daily dose administration rather than on a monthly basis. Additionally, the purpose of the chronic studies is to fully characterize the toxicity profile of icatibant over time as it may pertain to the anticipated human exposure. Jerini inquired about the dose and dose regimen for the

chronic studies. The Division relayed that the 6 and 9 month repeat dose toxicology studies could be designed to reflect the anticipated clinical dosing regimen rather than a standard daily dosing regimen. Jerini solicited input concerning additional nonclinical study designs and stated that these will be provided as draft protocols for discussion. The Division agreed.

2. *Based on the regulatory history of this IND, our evaluation of the toxicology studies conducted to date, and the severity of the proposed indication, we are willing to consider accepting the chronic toxicology and carcinogenicity studies as phase 4 commitments should the data not be available at a time that the other aspects of the application are deemed adequate for approval. However, we expect that the outstanding studies will be initiated promptly. We encourage you to submit any carcinogenicity protocols for CDER Executive Carcinogenicity Assessment Committee concurrence prior to study initiation.*

Discussion:
Jerini noted that the carcinogenicity protocols will be submitted via standard procedures through CDER's Executive Carcinogenicity Assessment Committee as soon as they are available.

3. *Qualify for safety any impurity and/or degradant that exceeds ICH Q3A and ICH Q3B thresholds.*

Discussion:

Jerini asked for confirmation that the threshold discussed for CMC issues ((b) (4) for peptides, Tides Conference of 2006) was acceptable for safety qualifications studies. The Division confirmed that a qualification threshold for impurities and /or degradants of (b) (4) for peptides was acceptable.

Question 2:

The effects of inhibition of bradykinin actions on the myometrium are well documented in the literature – abortion in early pregnancy and tocolysis in late pregnancy – and investigations into effects of icatibant in pregnancy and embryofetal development in mice, rats and rabbits have shown the potential for

uterine myometrial effects in early and late-stage pregnancy. A comprehensive package of reproductive toxicology studies, covering all aspects of reproduction from fertility to weaning and pup development, has been conducted with icatibant. This package is currently being supplemented with a bridging toxicokinetic study in rabbits, using the same strain of animals and the same dose levels as in the original embroytoxicity study in this species.

Jerini believes that the toxicokinetic study in rabbits will complete the reproductive toxicity package and that no further nonclinical studies to investigate the findings in pregnancy are necessary.

Does the Agency agree?

FDA Response to Question 2:

Based on the summary you provided in the pre-NDA briefing package, you will have adequately completed the reproductive toxicology battery to support an NDA submission. However, review of these studies is necessary to conclude that no further reproductive toxicology studies would be needed.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

2.4 BIOPHARMACEUTICS

Question 1:

Icatibant has been tested for its in vitro metabolic stability in the presence of dog and human liver microsomes and dog and human S9-fraction. Results have shown that the metabolism of icatibant is not dependent on cytochrome P450 (CYP450) pathways. (b) (4) ***The possible effect of icatibant on inhibition or induction of CYP450 isoenzymes has been investigated in vitro. The results indicate that icatibant would not inhibit or induce other compounds metabolized by the cytochrome P450 pathway. Additionally, protein binding of icatibant is low in man (44%).***

Since there is a low potential for drug-drug interactions with icatibant based upon its metabolic pathway, its low potential for CYP450 drug-drug

interactions, and low protein binding, no drug-drug interaction studies in man are required.

Does the Agency agree?

FDA Response to Question 1:

Yes, we agree, but this is subject to review of the data presented in the NDA submission.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 2:

At the recommendation of the Agency (Meeting Minutes March 1, 2005), Jerini has modified the special populations study JE049 #1103, a parallel design, placebo controlled study, using multiple doses of 30 mg subcutaneous administration of icatibant in 32 healthy young and elderly, males and females, to permit definitive QTc assessment. Modifications of the study design included the addition of continuous Holter monitoring with frequent ECG measurements including times around t_{max}. The central evaluation was performed by an expert cardiologist.

Does the Agency agree that this study serves as a thorough trial to show a lack of effect of icatibant on QTc?

FDA Response to Question 2:

We are unable to respond to this question at this time due to additional information recently received regarding Study #1103. Comments regarding your QT study (Study #1103) will be forthcoming.

Discussion:

Jerini stated that the response to this question has not been received and asked when feedback could be expected. The Division commented that a response was pending due to the review of the additional data by the Interdisciplinary Review

Team for QT studies and that the comments will be sent to Jerini as soon as the review is completed.

Question 3:

When Jerini commenced the development program for icatibant in HAE, limited information was available on the PK and metabolism of icatibant following intravenous and subcutaneous administration. Since that time, additional clinical and nonclinical experiences have shown that <10% of parent compound is excreted in the urine, including in a clinical study where a 3.2 mg/kg intravenous dose was infused over 1 hour.

Icatibant is extensively metabolized to two inactive metabolites, M1 and M2. In vitro receptor binding studies show that these metabolites have no activity at bradykinin B1 and B2 receptors. Both metabolites are excreted primarily by the kidneys.

For HAE, icatibant is given mainly as a single subcutaneous dose (although a small proportion (10%) of patients may require up to 3 doses during an HAE attack). Since icatibant is eliminated mainly by non-renal routes and the metabolites, while being excreted renally, are inactive, Jerini concludes that a study in subjects with renal impairment is not required.

Does the Agency agree?

FDA Response to Question 3:

Submit all available data as well as your justification for not conducting a renal impairment study to the NDA. See the Agency's guidance on renal impairment study for further information.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

2.5 CLINICAL

Question 1:

Icatibant has been in development for indications other than HAE (e.g. asthma, allergic rhinitis, post-operative pain). Due to the very low systemic exposure to

icatibant seen with routes of administration other than the intravenous and subcutaneous routes, Jerini does not intend to submit data or reports in the NDA for clinical studies where only intranasal, inhalation or intra-articular routes of administration were used. However, a written summary of the safety of icatibant in these studies will be included in Module 5, Section 3.5.4.

Does the Agency agree?

FDA Response to Question 1:

Yes, your plan is acceptable.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 2:

Jerini will pool safety data for phase 2 and phase 3 studies for HAE. For the pooled analysis of safety data, Jerini intends to include adverse events, laboratory tests and vital signs for these studies. Likewise, safety data from phase 1 studies will be pooled and analyzed separately and discussed in a separate section of the Integrated Safety Summary (ISS).

Does the Agency agree?

FDA Response to Question 2:

No, we do not agree. You may pool the safety data from the phase 3 studies for HAE in the ISS. However, present the data from your phase 2 study (Study 2101) separately in the ISS as you plan to do with the safety data from the phase 1 studies. When you pool your safety data from the phase 3 studies, present the data from the controlled portion of the studies separately from the open-label portion.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 3:

Jerini has conducted 2 studies where subjects with liver cirrhosis were administered icatibant (JE049#2001 and JE049#2002).

Jerini does not intend to include data from these 2 studies in the pooled safety analysis for the phase2/phase3 studies due to differences between populations. These studies will be discussed separately in the Clinical Summary and clinical study reports (CSR) will be included in Module 5.

Does the Agency agree?

FDA Response to Question 3:

Safety data from studies in patients with cirrhosis should be included in the ISS in a separate section.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 4:

The primary efficacy endpoint, the onset of symptom relief, has been agreed with the Agency to consist of a preset reduction on the VAS for the key symptoms ranging from 30 mm to 20 mm depending on the severity of the baseline VAS. 'Response' was defined as any value to the right of and below the line Y=6/7 X-16 with X≥30mm. SAPs for both phase 3 studies JE049#2103 (study under IND) and JE049#2102 (conducted in the EU, Switzerland and Israel) are included in Appendix 5.5.3.

In order to support the primary endpoint, comprehensive multiple secondary endpoints were used, e.g. symptom scores by subject and by investigator and time to event (onset of symptom relief as reported by subject and investigator), and the correlation confirmed by Spearman-Rank correlation coefficients. This will be discussed in the dossier.

Jerini believes that the VAS tool used in the HAE program has been sufficiently evaluated. A supportive study is currently ongoing (JE049#4102) and we expect to submit the report of this study during review. A study synopsis is included in Appendix 5.5.1.

Does the Agency agree?

FDA Response to Question 4:

All data needed to support the safety and efficacy of your drug product for the proposed indication should be included at the time of initial NDA submission. We believe the validity of the VAS tool is important to your clinical development program.

Discussion:

Jerini sought further guidance on how to proceed and factors to consider for validation. The Division stated that the Study Endpoints and Label Development (SEALD) and clinical review teams had previously provided comments on the PRO and the proposed PRO validation study. The Division did not have additional specific comments on the PRO or validation study, but recommended that all data supporting the PRO instrument should be completed and included for review at the time of NDA submission.

Question 5:

Jerini has performed 2 phase 3 studies, JE049#2102 (FAST-2) and JE049#2103 (FAST-1). The results from the 2 phase 3 studies are summarized in Section 4.4.5.2. Results from the pre-planned statistical analysis have previously been sent to the Agency in a letter dated October 9, 2006.

Jerini believes that these pivotal phase 3 studies demonstrate safety and efficacy of icatibant in the treatment of HAE attacks and support an application acceptable for filing.

Does the Agency agree?

FDA Response to Question 5:

A review of the summary of results included in the meeting package suggests that you do not have two confirmatory efficacy studies since FAST-1 failed to meet the pre-specified primary endpoint, time to onset of symptom relief. While your phase 3 studies appear adequate to support an application acceptable for filing, the adequacy of the phase 3 studies to support the approval of icatibant for the treatment of acute HAE attacks will be a review issue.

Discussion:

A summary of the results of the FAST-1 and FAST-2 studies was presented. Jerini stated that although FAST-1 did not demonstrate a statistically significant benefit over placebo on the primary endpoint, the data were generally supportive of icatibant's efficacy. In addition, Jerini indicated that cross-study comparison of FAST-1 and FAST-2 suggests that icatibant displayed similar efficacy in the two studies and that tranxeamic acid performed similarly to placebo.

The Division stated that an NDA submission usually includes at least two adequate and well-controlled studies demonstrating efficacy. One small study without replication is generally not adequate to support approval of an NDA. Furthermore, the use of an unapproved, active comparator rather than placebo in FAST-2 complicates interpretation of the results of FAST-2. For example, the clinical benefit attributed to icatibant in this study may actually be due to tranexamic acid exacerbating the patients' condition. In addition, open-label data is of limited utility as the natural history of an acute HAE attack is not well-defined. The Division cautioned Jerini about the amount of efficacy data expected to support approval and indicated that based upon the information available at this time, Jerini may not have enough efficacy data to support approval.

Question 6:

As summarized in Question 2, efficacy data proposed for presentation in the CTD have been obtained from an open-label phase 2 study using icatibant (study JE049#2101) and 2 randomized, controlled multicenter studies conducted using icatibant with either tranexamic acid (study JE049#2102; called FAST-2) or placebo (study JE049#2103; called FAST-1) as the controlled group. Jerini intends to integrate efficacy data for these HAE studies (s.c. groups of study JE049#2101 only and the pivotal phase 3 studies), as described in the reporting and analysis plan for the ISE (appendix 5.5.3).

Furthermore, Jerini intends to present as a separate report analyses of pooled phase 3 studies (JE049#2102 and JE049#2103) comparing icatibant with the combined comparator arms of both studies (placebo in JE049#2103 and tranexamic acid in JE049#2102) using a metaanalysis approach. The results of a preliminary more simple pooled analysis are shown in Table 3.3-3.

In the Section Clinical Studies of the label, Jerini intends to present the efficacy of icatibant using pooled data in tabular form.

Does the Agency agree with this approach?

FDA Response to Question 6:

We intend to review the data from each of the individual studies separately. If you plan to pool efficacy data in the ISE, you could pool data from the two phase 3 trials, but do not include data from the phase 2, open-label, non-controlled study.

Although you provided a table you plan to include in the proposed product label, a detailed discussion of the label is premature at this time.

Discussion:

The sponsor agreed to the Division's response, no discussion occurred.

Question 7:

Although clinical trials were conducted with the icatibant injection administered by the health care provider, Jerini intends (b) (4) [redacted].

Does the agency agree?

FDA Response to Question 7:

No, we do not agree. The product label will reflect the method of administration used in the clinical studies.

Discussion:

Jerini acknowledged the need for proper education on self-administration for both the physicians and patients. Jerini asked the Division to identify the Division's concerns regarding self-administration. The Division stated that given the potential life-threatening aspects of hereditary angioedema and the fact that early intervention with self-administration may affect the efficacy and safety profile of icatibant, clinical data demonstrating the efficacy and safety of self-administration

would be required. Patient education and data from open-label studies would not be sufficient to support self-administration.

2.6 eCTD

Question 1:

Jerini is unable to find any guidance on the FDA website regarding the requirement to enter metadata in document properties fields.

Can the Agency confirm that this is no longer required?

FDA Response to Question 1:

For information about data submissions, please check the CDER website at http://www.fda.gov/cder/regulatory/ersr/ectd.htm. Additional information may be obtained via esub@cder.fda.gov.

Discussion:

The sponsor agreed with the Division's response, no discussion occurred.

Question 2:

Jerini does not propose to submit any part of the submission on paper, but to provide the complete submission electronically. Legacy documents, such as studies conducted by the licensor (b) (4), will be provided as PDF files in the eCTD.

Does the Agency agree?

FDA Response to Question 2:

Your proposed plan is acceptable.

Discussion:

The sponsor agreed with the Division's response, no discussion occurred.

Question 3:

Jerini proposes to include for phase 3 studies all CRFs, Patient Profiles and datasets.

For all other sponsor initiated clinical studies, Jerini proposes to include CRFs and datasets for those patients who experienced SAEs, deaths, and AEs that resulted in early withdrawal from the study.

Jerini proposes not to include any patient data for (b) (4) legacy clinical studies.

Are these three proposals acceptable to the Agency?

FDA Response to Question 3:

We request you submit all CRFs, Patient Profiles, and datasets for your open-label, phase 2 Study JE049#2101. For all other sponsor-initiated clinical studies, your proposed plan to include CRFs and datasets for only those patients who experienced SAEs, deaths, and AEs that resulted in early withdrawal from the study is acceptable. Omission of data from the (b) (4) legacy studies is also acceptable.

Discussion:

The sponsor agreed with the Division's response, no discussion occurred.

Question 4:

The Jerini CSRs will be provided to the Agency tagged according to the STF file specification identifying the specific granules of the CSR.

Legacy (b) (4) CSRs will be tagged as legacy study reports.

Does the Agency agree?

FDA Response to Question 4:

Yes, your proposed plan is acceptable.

Discussion:

The sponsor agreed with the Division's response, no discussion occurred.

Question 5:

Can the Agency provide a point of contact for e-submission questions?

FDA Response to Question 5:

See response to eCTD Question 1.

Discussion:

The sponsor agreed with the Division's response, no discussion occurred.

Question 6:

Jerini intends to submit a pilot submission to the Agency for review and comment end of January 2007. A suggested ToC will be presented.

Could the Agency advise on their process and timeline for the evaluation of the pilot?

FDA Response to Question 6:

In general, pilot submissions are evaluated in 2 to 3 weeks. See response to eCTD Question 1 for specific details.

Discussion:

The sponsor agreed with the Division's response, no discussion occurred.

Additional Statistical Comments Regarding NDA Submission:

1. *Explain why you chose the Prentice-Wilcoxon test for your time-to-event analyses. Provide references and programming code in your NDA.*

2. *Provide details regarding the stochastic minimization procedure. Include covariates in your analyses for those factors you used to perform the minimization; consider subgroup analyses based on these factors.*

3. *Perform a life table analysis. Provide tables (SAS output) showing the number of patients at risk and the number of patients achieving relief.*

4. *Analyze, at each time-point, the VAS for the symptom used in the primary analysis and for each symptom where the patient's baseline VAS was 30 or greater. Also, graphically show for each patient the VAS for each parameter over time (i.e. 4 lines on each graph for each patient).*

5. *Provide Kaplan-Meier curves for time to symptom relief.*

6. *Provide graphs with individual patient data to demonstrate treatment differences on the symptom scores. Examples include boxplots of the symptom scores by treatment or cumulative distribution plots of the symptoms scores by treatment.*

Discussion:

No discussion occurred regarding the above statistical comments.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 SUMMARY

Listed below is the itemized summary provided by Jerini at the meeting's conclusion.

1. Jerini will submit their pediatric development plan for review prior to submission of the NDA application with the understanding that the plan may not be reviewed prior to NDA review.

2. The Division agreed that the specifications for impurity profiling set forth in the Tides Conference of 2006 are acceptable.

3. Jerini will conduct additional nonclinical studies to evaluate the chronic toxicity of icatibant. The protocols will be submitted for comment before finalization.

4. The Division will forward their response to Biopharmaceutical Question 2.

5. There is no additional guidance from the Division regarding Clinical Question 4. The Division recommended that all supporting data should be submitted in the NDA.

6. Regarding Clinical Question 5, Jerini acknowledged the Division's response and comments regarding the efficacy data.

7. Jerini noted that the open label design for self-administration is not adequate [redacted] (b) (4)

8. Jerini acknowledge that fileability of the NDA application will be determined once the NDA is submitted.

5.0 ATTACHMENTS AND HANDOUTS

Jerini handout attached.

Icatibant
Regulatory – History related to meeting

- Orphan Drug (Nov 25, 2003)
- Pre-IND meeting (Feb 6, 2004) DGCDP
- IND (Apr 8, 2004)
- Fast track (Jun 15, 2004)
- EOP2 CMC (Jul 2004)
- SPA JE049#2103 pivotal phase 3 (Jul 2004)
- Pre-NDA (Mar 1, 2005)
- IND reassigned to DPADP (Sept. 2005)
- Endpoint Evaluation 4102 (Sep, 2005)

Icatibant
Regulatory – Status of Icatibant

- HAE FIH
- Orphan Drug Designation (Nov 25)

- Type B Pre NDA meeting (Mar 1)
- Pharm. and Tox amend. (Jul 18)
- IND transferred to DPADP (Sep)
- Req f Evaluation of endpoint validation JE049 #4102 (Sep 8)

- Pre-NDA Meeting (Jan 24)

2003 → 2004 → 2005 → 2006 → 2007

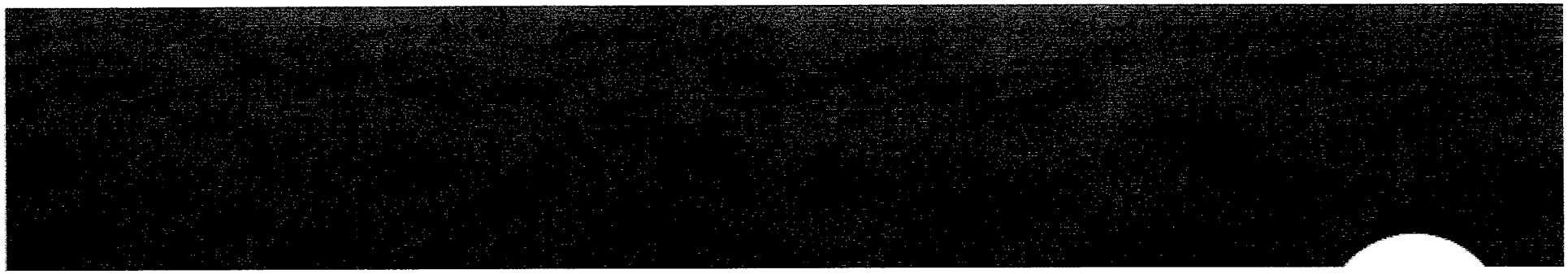
- IND to GCDP (Apr 8)
- Fast track designation (Jun 15)
- E0P2 CMC (Jul 1)
- SPA of JE049 #2103 (Jul 29)

- Final SAP JE049 #2103 (Oct 10)
- Proposed Trade Name Application (Oct 13)
- Information Amend. Toxicology, Safety, Pharmacology (Oct 23)
- Pre-NDA meeting request (Nov 23)
- Request for NDA number (Dec 13)
- CMC Amendment (Dec 14)
- Submission of Briefing Book (Dec 20)

JERINI

Icatibant
Regulatory – NDA Indication

- IND submitted to Division of DGCDP (Apr 8, 2004)
  'Treatment of acute attacks of hereditary angioedema by Icatibant acetate'
- Fast track designation (Jun 15, 2004)
  'Icatibant (JE049) subcutaneous for treatment of hereditary angioedema'
- Pre-NDA Meeting (Jan 24, 2007)
  Proposed Indication:
  Treatment of hereditary angioedema
- Submission planned Q2 2007



Icatibant: Nonclinical

- Additional comments

Program of Nonclinical studies (1)

- Icatibant is intended for treatment of a chronic intermittent disease manifested by acute attacks (HAE)
- The Nonclinical chronic safety program was designed to provide exposure overage relative to the clinical exposure on the basis of **dose level and frequency**.
- Clinical treatment regimen (based on 70 kg patient) will be:
  - No more than 3 x 30 mg injections/day (equiv to 1.3 mg/kg/day). Rat 10 mg/kg/day and dog 60 mg/kg/day.
  - No more than 8 x 30 mg injections/month (equiv to 3.4 mg/kg/month). Rat 300 mg/kg/month (**14x exposure**) and dog 900 mg/kg/month (**208x exposure**).

Program of Nonclinical studies (2)

- Although the Agency indicated that 6/9 month studies are typically needed to support a chronic exposure NDA, is this necessary for a chronic intermittent NDA?

Design Issues

- Frequency of dose – daily/multiple daily/intermittent per day?
- Sexual maturity – age of animals (particularly dogs)?
- Exaggerated pharmacology issues – avoidance of complex findings of no clinical relevance.
- Two species carcinogenicity studies?

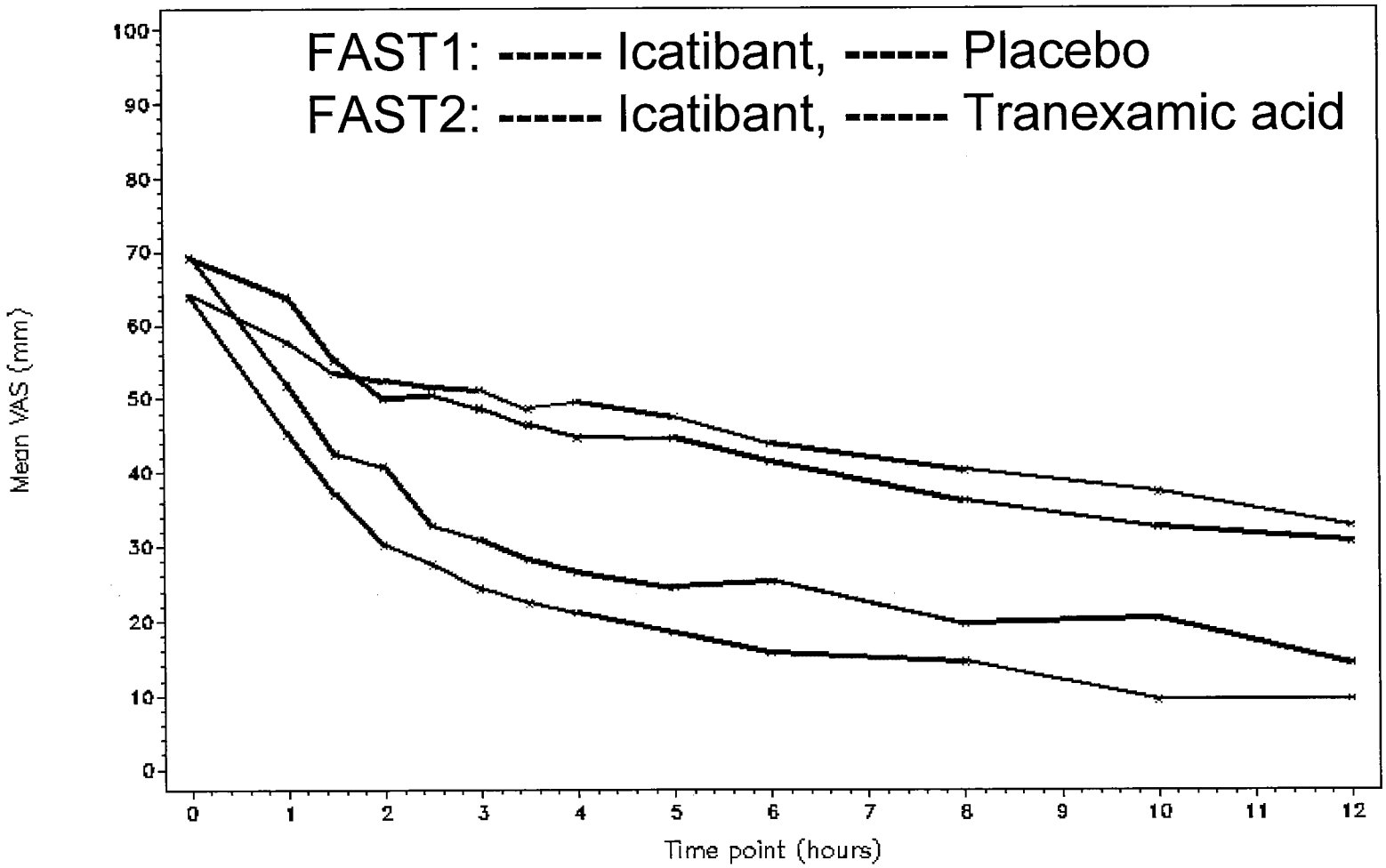
- **Further discussions are required urgently with the Agency to address these issues**

Icatibant: Clinical

- Question 5

JERINI

FAST Studies
Mean VAS Values (Primary Symptom)



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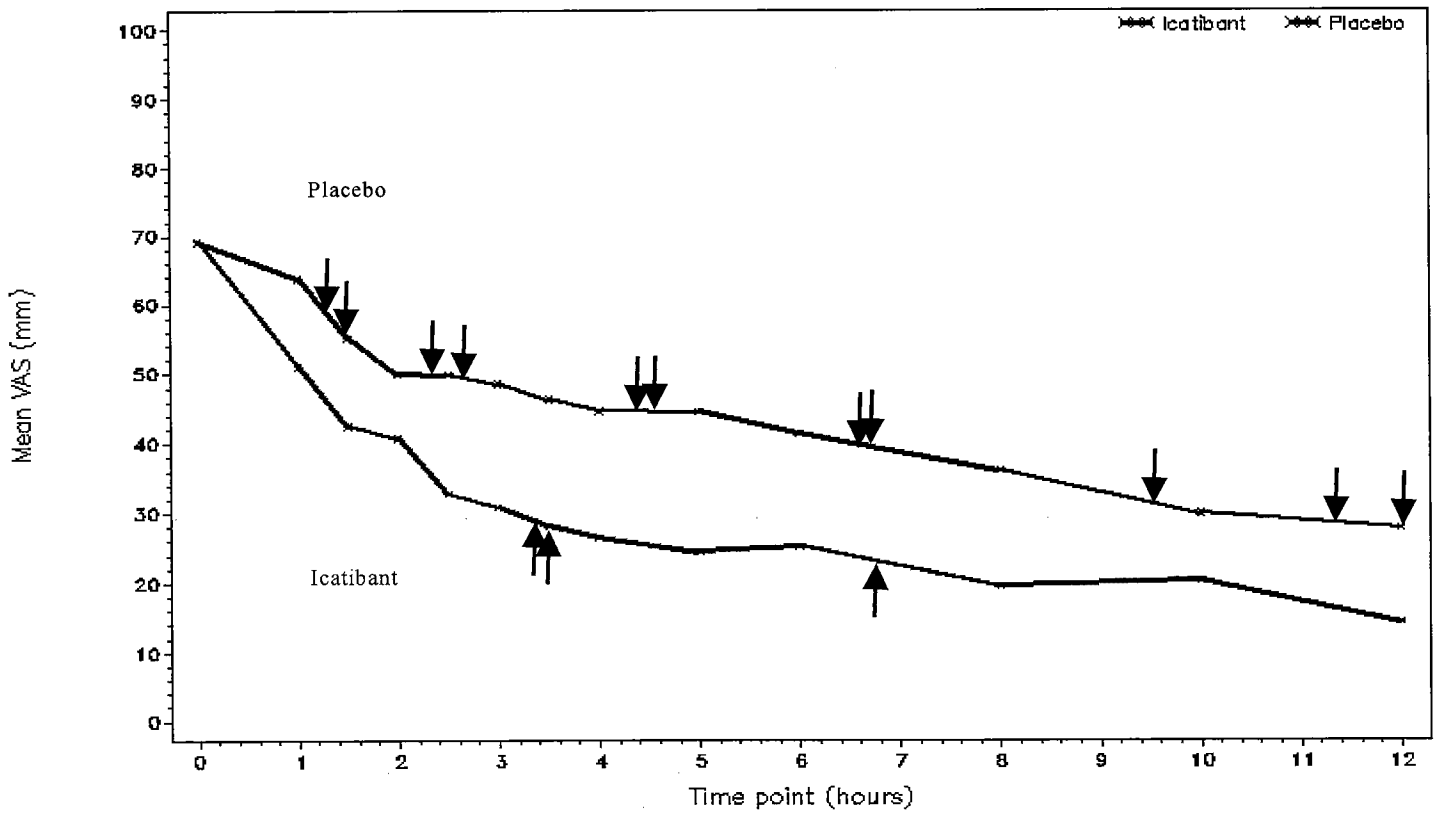
FAST Studies
Rescue Medication within 12 h (Controlled Phase)

	Icatibant	Placebo / Tranexamic Acid
FAST 1	3 / 27 (11.1 %)	11 / 29 (37.9%)
FAST 2	0 / 36 (0%)	6 / 38 (15.7%)

FAST 1
Rescue Medication within 12 h (Controlled Phase)

- Mean VAS Values, Primary Endpoint



Arrows show administration of first rescue medication

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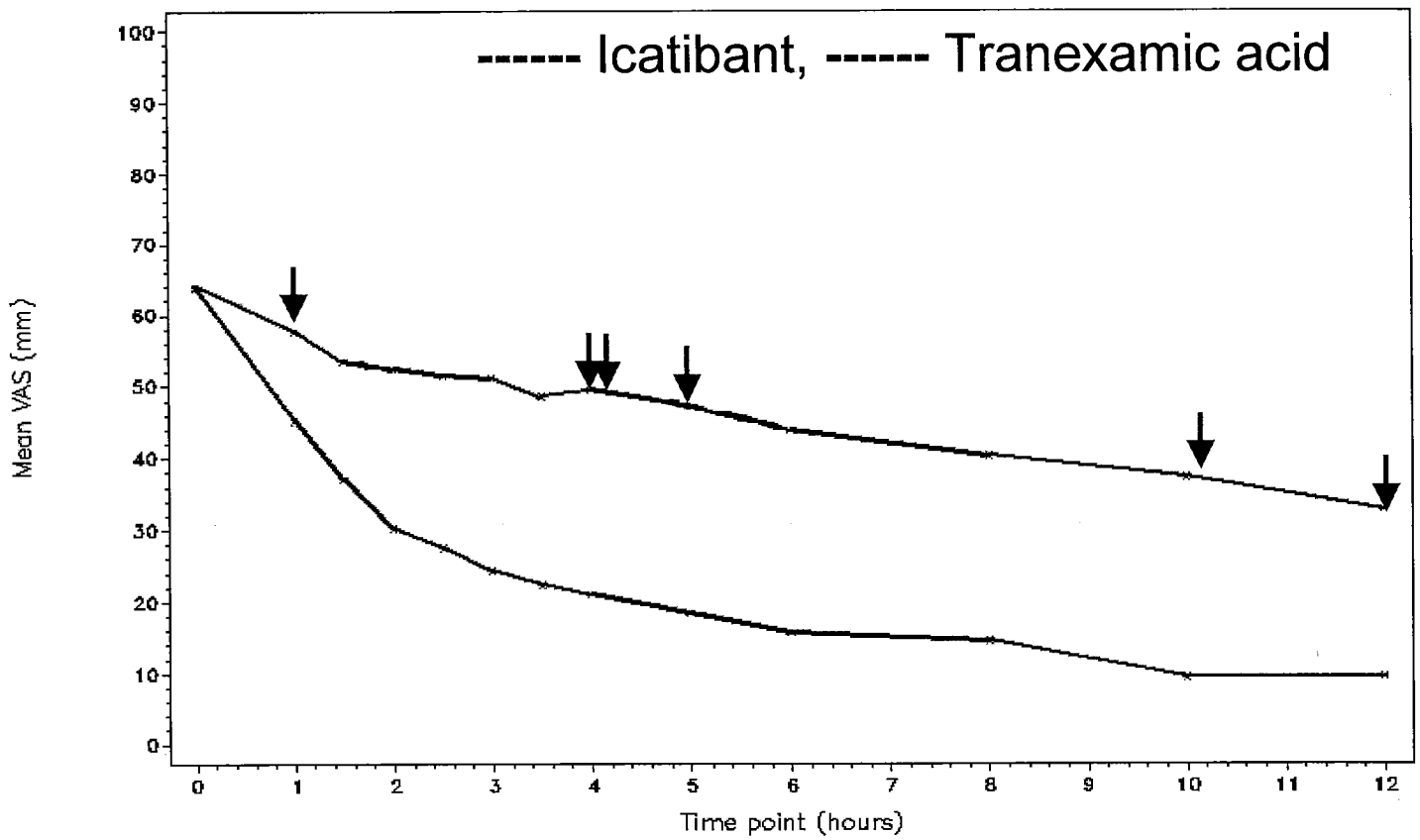
FAST 2
Rescue Medication within 12 h (Controlled Phase)

- Mean VAS Values, Primary Endpoint



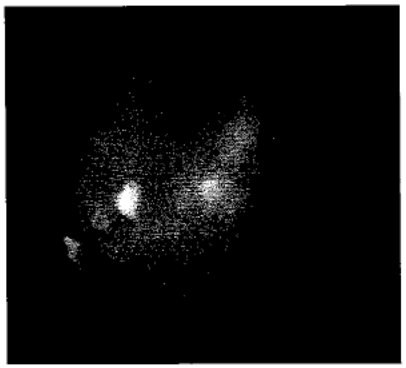
Arrows show administration of first rescue medication

JERINI

Laryngeal Edema Treated with Icatibant

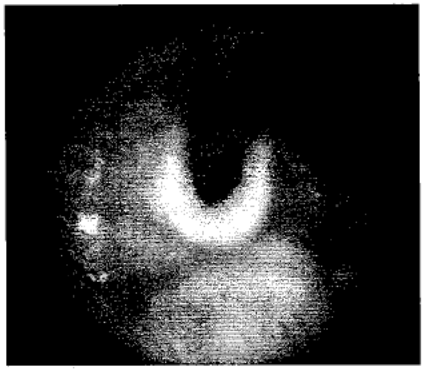
(b) (4) FAST-2)

0h

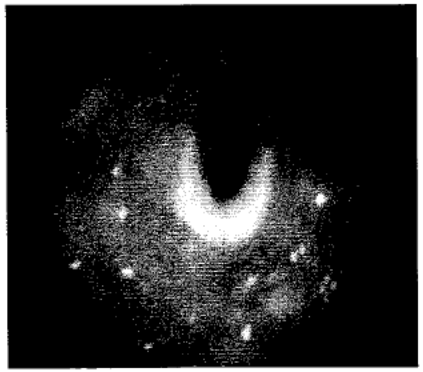


Icatibant administration

1h



2h



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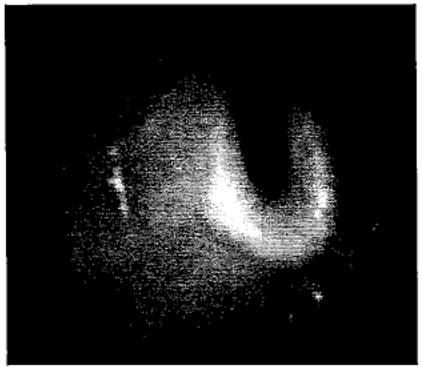

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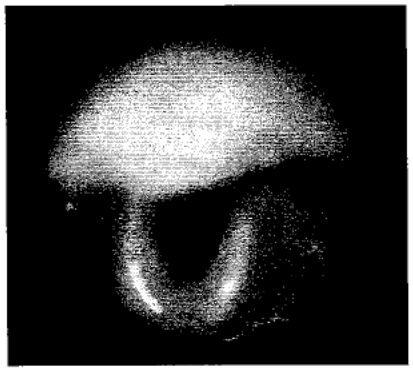


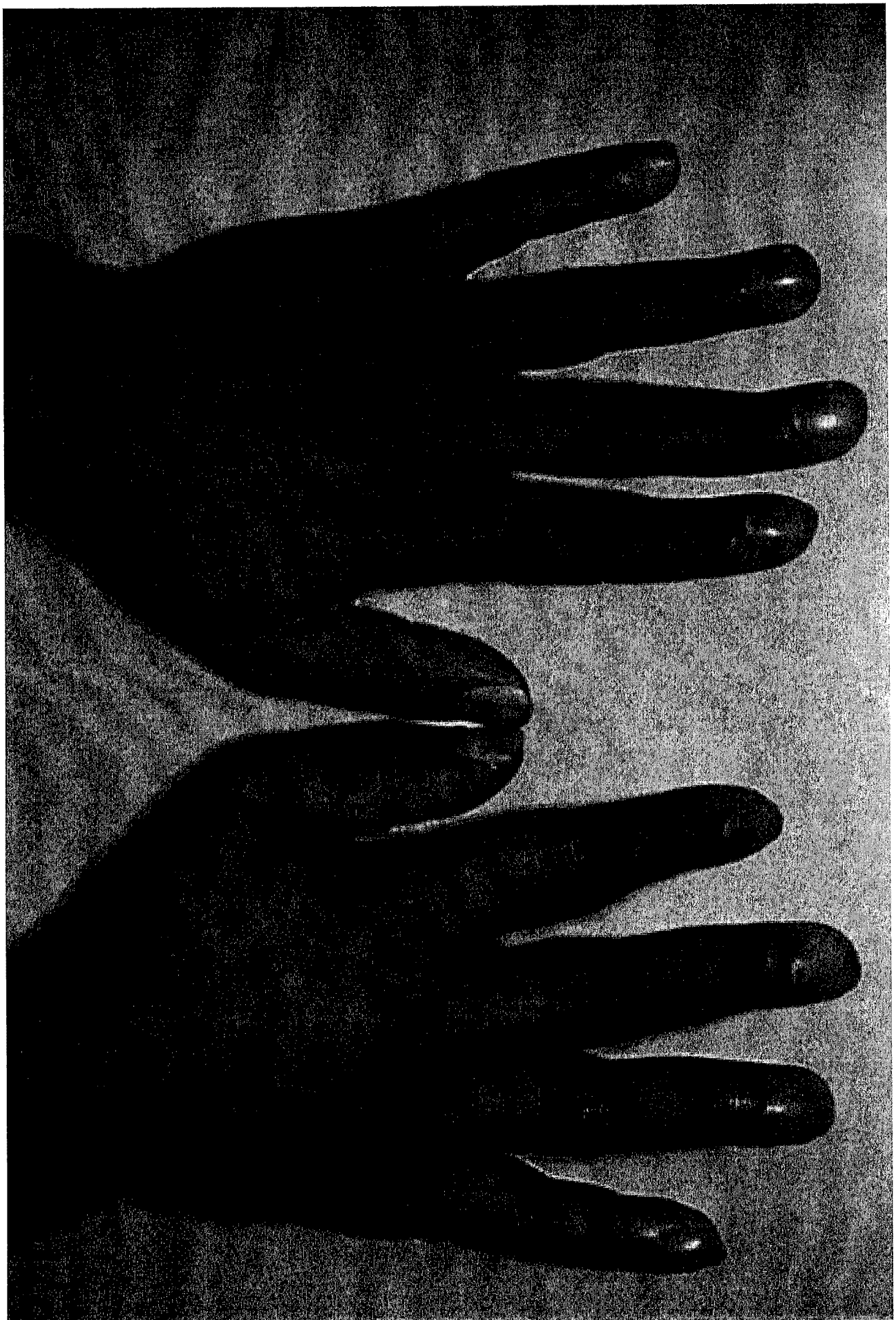
JERINI

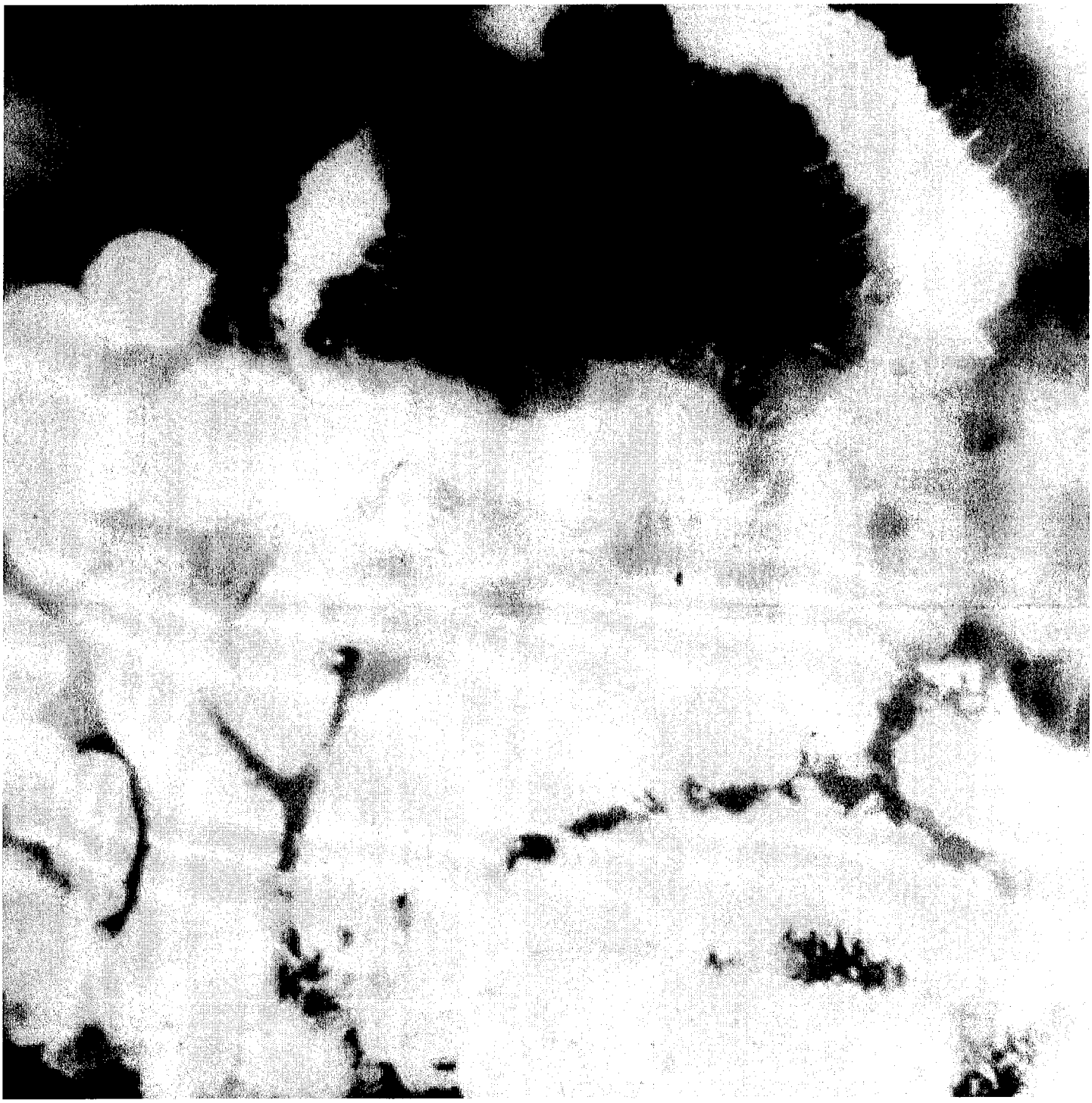
Thank you

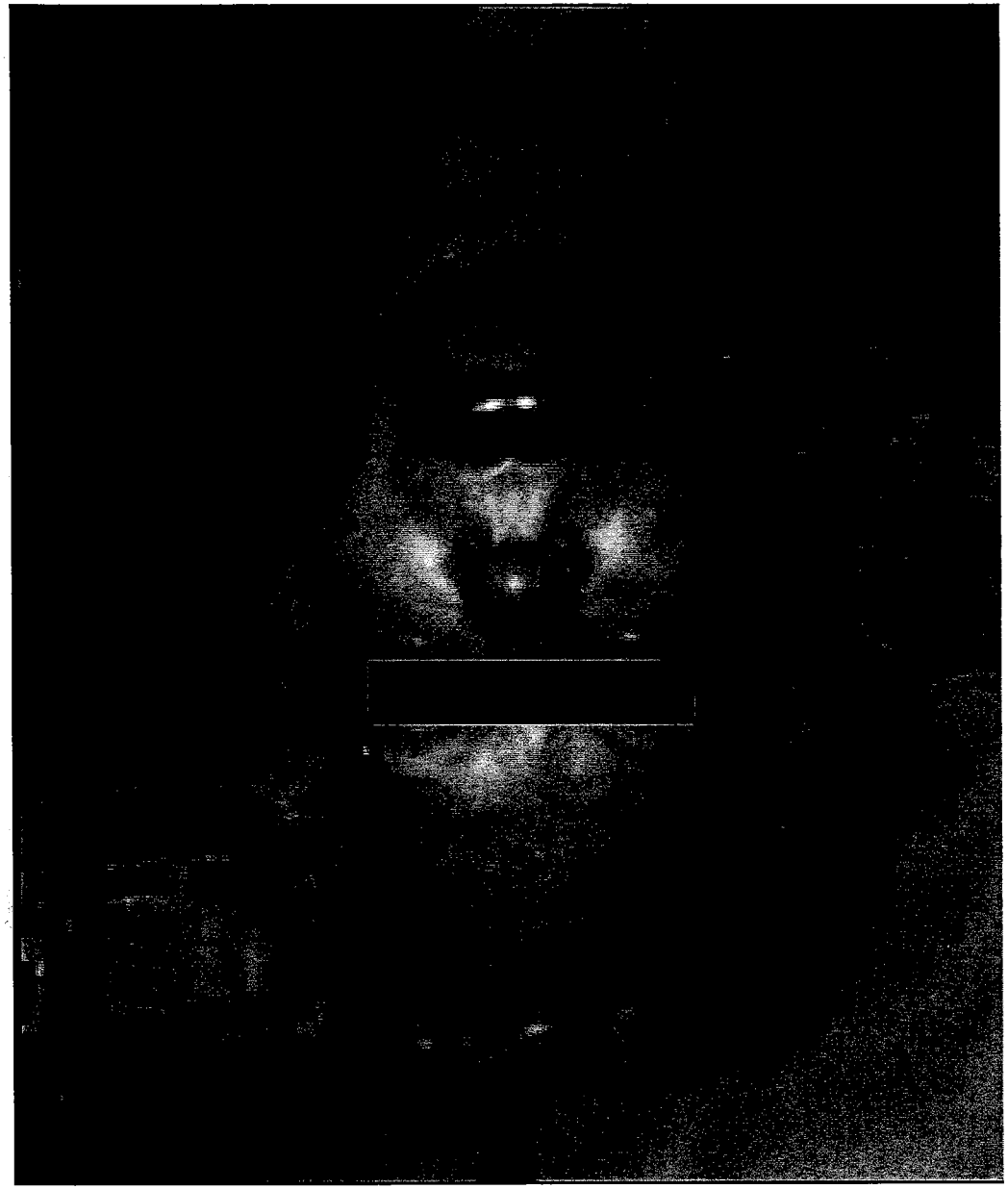
JERINI

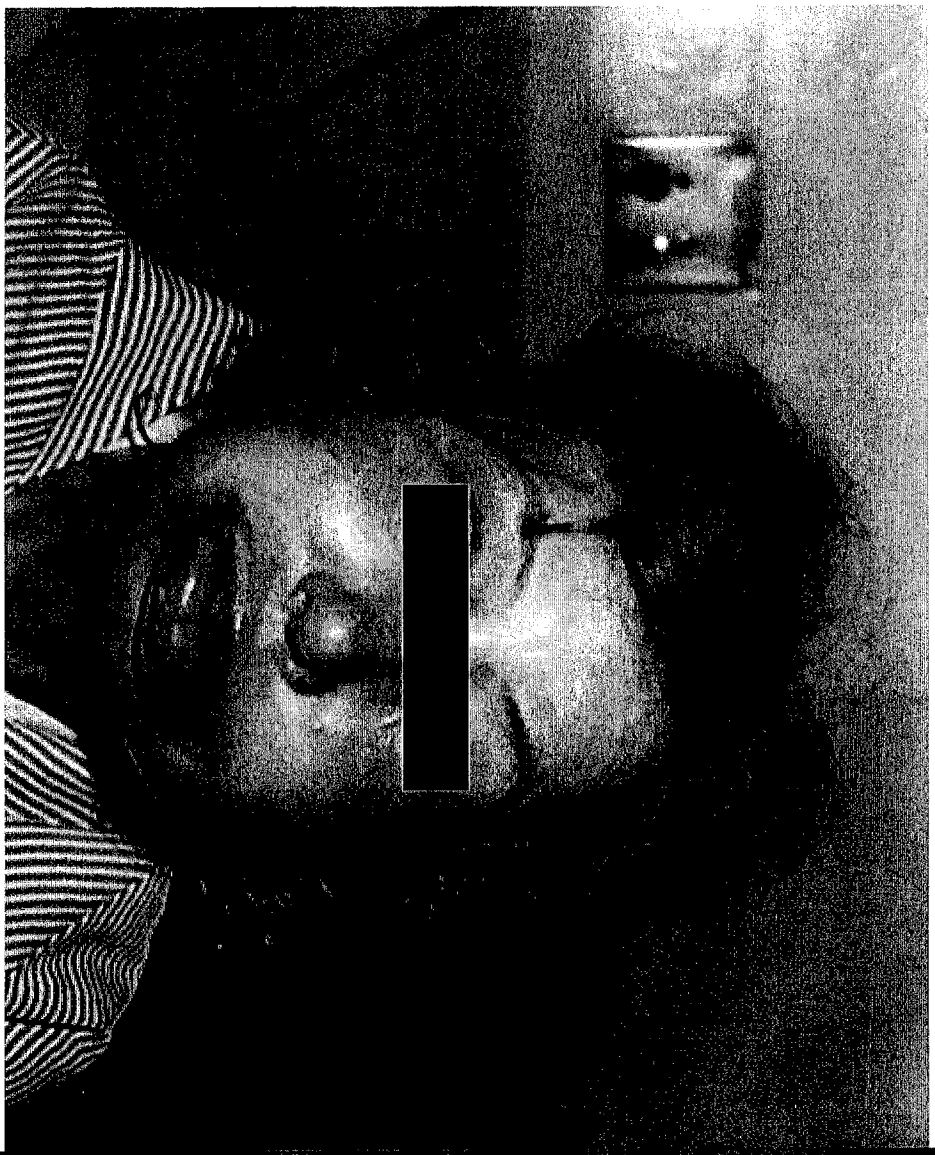
Hereditary Angioedema: Problems With Current Therapy

(b) (4)

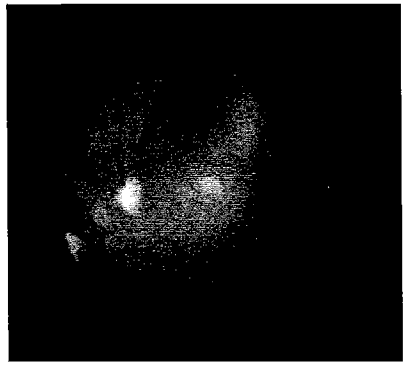








Laryngeal Edema



Tongue Swelling

Current Treatment of HAE in U.S.

Prophylaxis	-EACA -anabolic steroids	+ part population non-responders	Considerable long term toxicity Next slide
Manifestation of disease	**Treatment option**	**Effectiveness**	**Toxicity, side effects**
Cutaneous attacks	-Analgesics , -Antihistamines	poor	
Abdominal attacks	- Narcotics - Antiemetics	+ pain + nausea	Narcotic abuse
Laryngeal attacks	- Epinephrine - Intubation - Tracheotomy	+ +++ +++	

In US acute therapy is not adequate

- Anabolic steroids have numerous side effects, prolonged exposure accompanied with toxic side effects, can not be given to children and pregnant women
- Anabolic steroids and plasmin inhibitors like EACA do not have any clinical effectiveness for acute attacks
- Fresh frozen plasma may prove dangerous

Jerini Strategy for Measurement and Control of Impurities

- Icatibant is a synthetic decapeptide
- Jerini has followed the rationale in the ICH guidances Q3A(R) and Q3B(R) for the reporting and control of impurity classes
- The scope of these ICH guidances do not specifically address criteria for the measurement and control of peptide-related impurities

Peptide-Related Impurities

(b) (4)

[redacted]

JERINI

Products, Sources and Sites: An FDA Perspective – TIDES 2005

Products, Sources, and Sites:

Impurities Specifications

(b) (4)

Slide Notes

Slide 26 / 41 | Paused

00:05 / 00:05

Macromedia Breeze

JERINI

Drafted: Hill/2-12-07
Initialed: Fadiran/2-12&22-07
Peri/2-16&21-07
Fraser/2-16&21-07
Guo/2-12 & 22-07
Mele/2-12&22-07
Shea/2-15&21-07
McGovern/2-15&21-07
Limb/2-15&21-07
Seymour/2-15&21-07
Chowdhury/2-21-07
Finalized: Hill/2-22-07

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

/s/

Carol F. Hill
2/22/2007 06:07:00 PM

MEMORANDUM

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

TO: Sandy Barnes, CPMS
Division of Pulmonary and Allergy Drug Products, HFD-570

FROM: Brian Strongin, CPMS
Division of GI and Coagulation Drug Products, HFD-180

SUBJECT: Transfer of IND 68,214
Icatabant for the treatment of acute attacks of hereditary angioedema

In the line with the OND policy of placing administrative responsibility of NDAs within the Division that reviews the principal clinical research activity of the drug, we are forwarding the attached NDA for your acceptance. If you do not concur, please include the reason as a signature comment. If you have any questions, call me at 301-827-7459.

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

/s/

Sandra Barnes
8/18/2005 05:44:40 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,214

Jerini AG
c/o Target Health Inc.
Attention: Jules Mitchel, MBA, Ph.D., President
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Mitchel:

Please refer to the meeting between representatives of Jerini AG and the FDA on March 1, 2005. The purpose of the meeting was to discuss current clinical, toxicology, and CMC issues to support the NDA submission and to review answers provided to the agency (IND 68,214, Serial 006, submitted July 22, 2004) items #1, #3, and #4 in response to the FDA letter dated June 28, 2004, and the consideration of items #2 and #5.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Ryan Barraco, B.A., B.S.
Consumer Safety Officer
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 1, 2005

TIME: 12:00 PM 1:30 PM

LOCATION: Parklawn Building, 3rd Floor, Conference Room "C"

APPLICATION: IND 68,214
Icatibant (JE 049) S.C.

TYPE OF MEETING: Type B: Pre-NDA/Supplement

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Mr. Ryan Barraco

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Dr. Kathy Robie-Suh	Acting Deputy Director	Division of Gastrointestinal and Coagulation Drug Products (DGCDP) (HFD-180)
2. Dr. Jasti Choudary	Supervisory Pharmacologist	DGCDP (HFD-180)
3. Dr. Ronald Honchel	Pharmacologist	DGCDP (HFD-180)
4. Dr. Min Lu	Medical Officer	DGCDP (HFD-180)
5. Mr. Ryan Barraco	Consumer Safety Officer	DGCDP (HFD-180)
6. Dr. Ramesh Raghavachari	Chemist	Division of New Drug Chemistry II (HFD-820)
7. Dr. Tien-Mien Chen	Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation II (HFD-870)

EXTERNAL CONSTITUENT (Jerini AG and Target Health Inc.) ATTENDEES AND TITLES:

External Attendee	Title	Representing
1. Dr. Bernd Rosenkranz	Vice President Clinical Development	Jerini AG
[redacted]		
3. Ms. Andrea Ludwig	Project Manager, CMC	Jerini AG
4. Dr. Jochen Knolle	Chief Scientific Officer	Jerini AG
5. Claudia Julina	Head Drug Regulatory Affairs	Jerini AG
6. Dr. Jules T. Mitchel	President, Target Health Inc.	Jerini AG

(b) (4)

BACKGROUND:

Target Health Inc. submitted a Meeting Request (MR) for Jerini AG on January 5, 2005, received January 6, 2005, for a Pre-NDA/Supplement meeting for Icatibant (JE 049) S.C. The sponsor submitted eight questions addressed to the Agency. Jerini AG requested the Pre-NDA meeting to discuss current clinical, toxicology, and CMC issues to support the NDA submission and to review answers provided to the agency (IND 68,214, Serial 006, submitted July 22, 2004) items #1, #3, and #4 in response to the FDA letter dated June 28, 2004, and the consideration of items #2 and #5.

MEETING OBJECTIVES:

To reach an agreement with the Agency on the responses to the questions posed in the sponsor's background package (submitted January 28, 2005, received February 1, 2005).

DISCUSSION POINTS:

In response to the sponsor's questions in their background package for the meeting, the following agreements were reached after discussion. The format provides for the sponsor's questions, followed by the Agency's responses in bold lettering. The sponsor's presentation slides follow the questions and responses.

IND 68,214 Icatibant (JE 049)
Pre-NDA/Supplement Meeting
March 1, 2005

<u>Questions and Responses</u>:

7.1 Clinical

7.1.1 Cardiovascular QTc prolongation

Jerini has performed a careful assessment of the possible effect of Icatibant on cardiac repolarization in in vitro and in vivo preclinical studies, and in clinical studies in healthy subjects as well as in patients with liver cirrhosis. The evaluation of the effect of the drug on QTc in patients with HAE (study JE 049 #2101) is ongoing, and QTc evaluation has been included in the ongoing pivotal registration studies in HAE patients. It should be noted that all ECGs have been processed at the same central laboratory (b) (4) (b) (4) using validated procedures.

The available data (Attachment 1) do not give any indication of the effect of the drug on cardiac repolarization. Furthermore, the intended treatment regimen for Icatibant in acute attacks of HAE will be repeated single injections, instead of a regular, chronic treatment. Considering the seriousness of the orphan indication hereditary angioedema, the benefit for the patient by providing a drug to alleviate symptoms is considered to outweigh the potential, but not demonstrated, risk of QTc prolongation. Therefore, Jerini does not intend to conduct a specific phase I study to assess the effect of Icatibant on QTc interval.

Does the agency agree to this approach?

Agency Response:

- **The ICH E14 guidance recommends that studies should characterize the effect of a drug on the QT/QTc throughout the dosing interval and care should be taken to perform ECG recordings at time points around the C_{max}. In the studies you have performed, the ECG monitoring was done only at certain time points, e.g., 1, 2, 4, 6… 24, 36, 48 hrs post dosing. As such, the maximum changes in QTc at/near the peak time for C_{max} after IV (at the end of infusion) or SC (at around 0.6-hr postdose) were not available. It is recommended that QTc data be collected and analyzed in the proposed PK study JE049# 1103. Include additional time points at or near the C_{max}.**

- **Sponsor presented an outline of proposed study to evaluate QTc prolongation (Study JE049, #1103). See sponsor's slide, page 2. The proposal appears acceptable.**

7.1.2 Dose selection rationale

In term of dose-ranging study, Jerini has performed three studies (JE049 #1001, 1102 and 2101, Attachment 2), which Jerini feels will properly identify an appropriate dose to support the subcutaneous (SC) route of administration. The studies are summarized in the following section.

7.1.2.1 PK-PD Data in Healthy Subjects (Protocol JE049 #1001)

This study addresses the safety, tolerance, renal function and pharmacokinetic/ pharmacodynamic profile of Icatibant after a continuous IV infusion. The report on the safety, tolerance and pharmacodynamic results can be found in IND (b) (4), Volume 13. The final draft report on plasma PK data is included in Attachment 2.1 of the briefing package.

7.1.2.2 Phase I Bioavailability Study (Protocol JE049 #1102)

Study JE 049 #1102 is a randomized, double-blind, placebo-controlled, crossover, single dose study designed to investigate the absolute bioavailability, safety and tolerability of subcutaneous (SC) doses of Icatibant. Single subcutaneous injections of 0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg were initially given to assess local tolerability. Thereafter, the pharmacokinetics of single IV injections of 0.4 mg/kg were compared to single SC injections of 0.4 mg/kg Icatibant given at 2 different concentrations (10 mg/mL and 20 mg/mL in 12 subjects each). SC injections showed a bioavailability of approximately 90%. Maximum concentrations were reached after approximately 30 min. Local reactions were noted in all active treatment groups. Symptoms included short-lived itching, burning sensation, and swelling as well as erythema. All symptoms were mild

and resolved spontaneously. The final report for this study is submitted to the IND, serial 010, and the report is included in Attachment 2.2.

7.1.2.3 Proof-of-Concept Study (Protocol JE049 # 2101)

This proof-of-concept-study in patients with a history of HAE followed an open design with the following treatment regimens/groups: 0.4 mg/kg infused intravenously over 2 or 0.5 hours, 0.8 mg/kg infused intravenously over 0.5 hours, 30 mg or 45 mg given by subcutaneous injection. The clinical symptoms of the treated edema episodes were evaluated by using questionnaires, visual analogue scales, symptom scores, and photo-documentation. Treatment with Icatibant shortened the time to onset of symptom resolution (median time between treatment start and symptom resolution as reported by the patient: 1.5, 1.2, 1.1, 0.5, and 0.4 hours for treatment groups 1-5, respectively). Upon treatment, duration of the attacks was considerably shorter than that of previous attacks. Icatibant was well tolerated. No difference between the treatment groups could be discovered.

The interim summary of clinical data for this study is enclosed in Attachment 2.3.

7.1.2.4 Rationale for the selected dose for the pivotal trial

The rationale for the selected dose in the clinical trial is based on preclinical data, clinical pharmacokinetic/pharmacodynamic (Phase I) information (study JE 049 #1001, Attachment 2.1) as well as the efficacy outcome gathered in the initial proof-of-concept study described above (JE 049 #2101, Attachment 2.3). Although in some of these studies Icatibant was administered IV, the data are appropriate to justify the SC dose, as comparable bioavailability of both routes of administration was demonstrated (JE 049#1102, Attachment 2.2).

In vitro studies regarding receptor binding and cellular effects have shown that the IC_{50} is approximately 1-10 nM. This information is consistent with the EC_{50} calculated from pharmacokinetic/pharmacodynamic data in study JE 049 #1001, in which an EC_{50} for the antagonism of the bradykinin-induced increase in cutaneous blood flow has been estimated as approximately 7.2 nM (9.4 µg/L). In a Phase I bioavailability study (JE 049 #1102), Cmax values are about 3.0 µM after infusion of a dose of 0.4 mg/kg over 0.5 hr. After administration of a dose of 0.4 mg/kg of 10 mg/mL solution by the SC route, Cmax values of 1.5 µM have been observed. These levels can be expected to be sufficiently high in order to antagonize the elevated systemic bradykinin concentrations during an angioedema attack, which have been reported to be approx. 50 pM, a level which is about tenfold higher than physiological bradykinin concentrations. Furthermore, concentrations remain elevated above 20 nM (which is roughly the IC_{50} value as described above) for about 6-8 hours. As a consequence, the bradykinin antagonist effect of Icatibant lasts for up to about 10-12 hours after single administration of a dose of 0.4 mg/kg. Finally, clinical efficacy of Icatibant has been demonstrated after a single administration of 0.4 mg/kg by i.v. infusion over 0.5 or 2 hours. Taking into account the almost complete bioavailability

(approximately 90%) of Icatibant after SC injection, a dose of 30 mg (i.e., 0.4 mg/kg in subjects of 75 kg body weight) given by SC administration is justified for the planned clinical efficacy trial. This prediction has been confirmed by the proof-of-concept trial in HAE patients (JE049 # 2101) in which the doses of 30 and 45 mg have been tested and both doses have shown to be effective.

Furthermore, a concentration of 10 mg/mL has been selected based on the outcome of study JE049 #1102, due to the increased severity of local reactions at higher concentrations. The injection volume of 3 mL has been proven to be acceptable to angioedema patients for the treatment of acute attacks. Higher volumes are considered to be less convenient for the patient. The maximum single SC dose of 30 mg administered as 3mL volume is clinically feasible.

Considering the small populations available for this orphan indication, the above data is considered sufficient to support the appropriate clinical dose.

Does the agency agree that the dose selection rationale is sufficient?

Agency Response:

- **The proof-of-concept study (JE049#2101) was an open-label, non-randomized study. There was no placebo group in the study. The results on pages 239 and 241 of the background package appear to be somewhat different with regard to onset of symptom relief. The preliminary results appear to show no differences among 5 dose regimens based on VAS scores. From these data it is not clear that the 30 mg SC dose is an appropriate dose for Phase 3 pivotal trials.**
    - **The sponsor presented a discussion of dose selection. The sponsor will provide a detailed summary of the rationale for the dose selection. The sponsor also clarified that the 30 mg SC fixed dose is intended to be the dose studied in the clinical trials with up to 3 doses of 30 mg given within a 24 hour period at six hour intervals if necessary. The sponsor stated they have 3 month rat and 3 month dog toxicology studies underway and estimate that results from those studies should be available around September 2005.**
- **Please clarify the headings on the table shown on page 241.**

7.1.3 Special Populations

To address the tolerability of Icatibant in special populations, Jerini plans to conduct a study on pharmacokinetics and tolerability of a single subcutaneous dose of Icatibant administered to healthy young and elderly, male and female subjects. As a secondary objective, the potential of Icatibant for antibody formation will be addressed.

The study outline is enclosed in Attachment 3.

Does the agency consider the planned study sufficient to address the subject of special population requirement to support the NDA?

Agency Response:

- **Your proposed study appears acceptable. However, in addition, you should also analyze your data from studies JE049 #2001 and JE049 #2002 according to the severity of hepatic impairment (i.e., mild, moderate, or severe) based on Child-Pugh scores.**

- **Some information in pediatric patients may be needed (e.g., PK, clinical, safety, etc.).**

  - **The sponsor described the plan for addressing pediatric use (See slide 10). This is planned for postmarketing development.**

7.2 Pharmacology/Toxicology

7.2.1 In-Vitro PK Strategy

A series of in vivo studies in several animal species has identified two major metabolites, M1 and M2, following cleavage of the Icatibant molecule. These metabolites have also been confirmed in man, both circulating in plasma and excreted in urine.

An in vitro study with dog and human liver microsomes showed no or negligible metabolism. Studies with dog and human liver S9 fractions showed a slow metabolism. When rat and human liver S9 fractions were exposed to Icatibant radiolabelled in the M1 portion of the molecule, the sum of unchanged Icatibant and M1 accounted for all the radioactivity present. The metabolism by S9 fractions and the lack of metabolism by microsomes, suggest the involvement of cytosolic, NADPH independent enzymes, probably peptidases (given the structure of Icatibant). In partial confirmation of this, Icatibant radiolabelled in the M1 portion of the molecule produced M1 when incubated with rat kidney enkephalinase.

These data are consistent with the non-involvement of cytochrome P450 isoenzymes in the metabolism of Icatibant and potential pharmacokinetic interactions with other agents affecting P450 isoenzymes are thus unlikely. It is now planned to study the possible effect of Icatibant in inducing or inhibiting a range of P450 isoenzymes. These studies will be performed in vitro with human liver microsomes (inhibition studies) or human hepatocytes (induction studies) using specific markers for the isoenzymes being investigated. Given that these inhibition and induction studies do not indicate any potential for interactions, no further studies are planned.

Does the agency agree that this program is sufficient to establish the potential for pharmacokinetic interactions with Icatibant?

Agency Response:

Your proposed program appears to be reasonable; however, this opinion is subject to the details of data which have not yet been submitted. Please submit the reports of your pre-clinical studies as outlined in the February 6, 2004 meeting minutes prior to the initiation of Phase 3 studies. These include the genotoxicity studies, teratology and fertility studies, and safety pharmacology studies.

7.2.2 Bridging of toxicology studies based on a modified manufacturing process

The final manufacturing process is a [redacted] (b) (4) as opposed to the manufacturing process during development, applied for most batches used in toxicological studies. [redacted] (b) (4). All batches conform to the specification for the drug substance.

The impurities found in batches manufactured by both methods are shown in the 'Comparative table of impurities (Attachment 4). For the batches manufactured according to the final process, known impurities were found at different levels, some higher and some lower than in earlier batches (earlier process). New impurities were detected by HPLC, all below the threshold of [redacted] (b) (4) for unknown impurities, within the limits of the specification.

Jerini plans to use one of the recent batches (final process) in the planned 3-month toxicology study in the rat and to perform additional genotoxicity studies (gene mutation in bacteria and chromosome aberration in mammalian cells) with the new material.

As the specification remains unchanged and one of the most important long-term toxicological studies will be performed with the new material, Jerini considers the new impurities as qualified.

Does the agency agree that the planned development program qualifies all impurities from the new manufacturing process?

Agency Response:

- **Your proposed program to qualify the impurities appears adequate.**
- **Provide data to differentiate the impurities obtained in** [redacted] (b) (4) **(also see response to question 7.3.3)**
- **You state that the final manufacturing process is a** [redacted] (b) (4) **Please specify when the process change will be made. Phase 3 studies and study JE049 #1103 should be conducted using the to-be-marketed drug product.**
    - **The sponsor clarified that the process change has been made.**

- **The proposed bridging toxicology program should be carried out prior to initiation of Phase 3 studies.**

7.3 Chemistry Manufacturing and Controls Issues

7.3.1 Stability program for pre-filled syringes

In addition to the ampoules used in clinical trials, Jerini is developing a pre-filled syringe. While the stability programme for ampoules was presented earlier and agreed upon by the agency, Jerini intends to present the stability program for the pre-filled syringes.

The stability program for pre-filled syringes is included in Attachment 5.

Does the agency agree with the stability protocol for the pre-filled syringe?

Agency Response:

The stability protocol provided appears to be acceptable. We recommend you include the syringe fill-volume as a part of the stability protocol.

7.3.2 Availability of stability data for NDA submission

At the time of submission of the CMC section of the NDA, 12-month data will be available for the ampoules, whereas three months data will be available for the pre-filled syringes. Considering the benefit of the patients to be able to self-administer the drug in pre-filled syringes, Jerini proposes to submit the CMC part with the available data and to submit the six-month stability data upon availability.

Does the agency agree to accept the submission of the CMC part with only three months stability data for the pre-filled syringes and accept additional data packages as soon as they become available?

Agency Response:

In general, 12-month real time stability data is recommended (please refer to ICH Guidance Q1A). Assignment of expiry dating period for the drug product may depend upon the real time stability data and the totality of the NDA submission (e.g., analytical, validation, impurity, etc.).

7.3.3 New manufacturing process - impurities profile

Analytical efforts will be made to identify and specify organic impurities. Considering that Icatibant is a synthetic decapeptide, Jerini would like to ask the agency for advice as to which threshold impurities should be identified. Jerini proposes to identify and specify all impurities that reach a threshold of (b) (4) in one of the registration batches.

Does the agency agree that the description of the organic impurities is sufficiently addressed?

Agency Response:

- **Provide data on impurities obtained from the** (b) (4) **in a tabular form. Indicate the new impurities and their levels in the new manufacturing process. Validate the analytical methods in which all these impurities would be identified during the manufacturing process.**

- **Provide information on lots manufactured by** (b) (4) **used for preclinical studies and clinical Phase 2 and Phase 3 studies.**

Additional comments:

General:

You should request an additional meeting with DGCDP after you have submitted your pre-clinical study reports and the study report for your Phase 2 study before submitting your NDA.

CMC:

Drug product specifications should include the following:

- **Volume in the pre-filled syringe**
- **Refer ICH Guidance Q6A for 'Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.'**
- **We would like to remind you of our recommendations at the End of Phase (EOP)-2 meeting on July 1, 2004.**

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

/s/

Ryan Barraco
3/22/05 02:41:40 PM

Kathy Robie-Suh
3/23/05 11:12:44 AM
signing for Dr. Joyce Korvick

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,214

Jerini AG
c/o: Target Health Inc.
Attention: Jules Mitchel, MBA, Ph.D., President
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Mitchel:

Please refer to the meeting between representatives of Jerini AG and the FDA on July 1, 2004. The purpose of the meeting was to review the Icatibant (JE 049) Subcutaneous (S.C.) CMC section.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Ryan Barraco, B.A., B.S.
Consumer Safety Officer
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 1, 2004

TIME: 11:30 AM 12:30 PM

LOCATION: Parklawn Building, 3rd Floor, Conference Room "C"

APPLICATION: IND 68,214
Icatibant (JE 049) S.C.

TYPE OF MEETING: Type B: End-of-Phase 2

MEETING CHAIR: Dr. Ramesh Raghavachari

MEETING RECORDER: Mr. Ryan Barraco

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Dr. Blair Fraser	Deputy Director	Division of New Drug Chemistry II (DNDCII) (HFD-820)
2. Dr. Liang Zhou	Chemistry Team Leader	DNDCII (HFD-820)
3. Dr. Ramesh Raghavachari	Chemist	DNDCII (HFD-820)
4. Mr. Ryan Barraco	Consumer Safety Officer	Division of Gastrointestinal and Coagulation Drug Products (DGCDP) (HFD-180)

EXTERNAL CONSTITUENT (Jerini AG and Target Health Inc.) ATTENDEES AND TITLES:

External Attendee	Title	Representing
1. Dr. Bernd Rosenkranz	Vice President Clinical Development	Jerini AG
(b) (4)		
3. Ms. Andrea Ludwig	Project Manager, CMC	Jerini AG
4. Dr. Jules T. Mitchel	President	Target Health Inc.

BACKGROUND:

Target Health Inc. submitted a Meeting Request (MR) for Jerini AG on April 21, 2004, received April 22, 2004, for a End-of-Phase 2 (EOP2) meeting for Icatibant (JE 049) S.C. The sponsor submitted three questions addressed to the Agency. Jerini AG requested the EOP2 meeting to discuss the CMC section. When the background package was submitted, the sponsor proposed five questions to the Agency.

MEETING OBJECTIVES:

To reach an agreement with the Agency on the responses to the questions posed in the sponsor's background package.

DISCUSSION POINTS:

In response to the sponsor's questions in their background package for the meeting, the following agreements were reached after discussion. The format provides for the sponsor's questions, followed by the Agency's responses in bold lettering.

IND 68,214
Icatibant (JE 049) subcutaneous (S.C.)
Jerini AG

Questions and Responses:

2.1 Specification for the Drug Substance associated with the Acceptance Criteria and the Analytical Procedures

Does the agency agree with the specification presented in table 2.1?

Agency Response:

The specifications for the drug substance appear to be acceptable.

However, see comments below:

1. **Tighten the proposed acceptance criteria for the product-related impurities based upon the batch test data acquired during product development.**

2. **Tighten the proposed acceptance criteria for process-related impurities, residual solvents based upon the batch test data acquired during product development.**

3. **Tighten the proposed acceptance criteria for process-related impurities, heavy metals based upon the batch test data acquired during product development.**

(please see additional comments)

2.2 Specification of the Drug Product associated with the Acceptance Criteria and the Analytical Procedures

Does the agency agree with the specification presented in table 2.2?

Agency Response:

The specifications provided for the drug product appear to be acceptable. Please include test method codes, in a separate column, for each specification on the sheet.

(please see additional comments)

2.3 Primary Stability Protocol for the Drug Substance

Does the agency agree with that protocol?

Agency Response:

The stability protocol provided for the drug substance appears to be acceptable.

2.4 Primary Stability Protocol for the Drug Product (packaging materials: glass ampoules and glass vials with rubber stopper)

Does the agency agree with the stability protocol according attachment C and the below mentioned procedure for the alternative packaging material?

Agency Response:

The stability protocol provided for the drug product appears to be acceptable.

2.5 Primary Stability Protocol for the Drug Product (packaging material: glass ampoules and pre-filled syringes)

Is a comparative study as described below acceptable as the primary stability protocol for ampoules and pre-filled syringes?

Agency Response:

No. Primary stability data for the pre-filled syringes need to be submitted. In general, 12-month primary stability data, for drug product in the intended final container, is needed for NDA submission. Additionally, provide a citation for the 510k for your syringe or DMF references for the syringe and components.

Additional Comments:

Drug Substance:

- **Develop (b) (4) HPLC methods to provide control of the (b) (4) of starting materials used in the (b) (4)**
- **The acetic acid content in the drug substance acceptance criteria (b) (4) appears to be very high, please clarify.**
  - **The sponsor will plan for the final specifications to include the acetate salt and for the base.**

- **Provide additional characterization for the drug substance (e.g.):**

(b) (4)

  - **Please establish a reference standard that reflects the product used for preclinical studies.**
  - **We recommend that a biological assay be developed to fully characterize the reference standard.**
    - **The sponsor will evaluate this recommendation and may provide an alternative proposal.**

- **Impurities:**
  - **Explain the peak at** (b) (4) **in your mass spectrum.**
  - **Drug substance structural elucidation by** (b) (4) **should be elaborated. Data should be provided in a tabular form for ease of review.**
  - **Alternate** (b) (4) **HPLC methods should be used to demonstrate the separation and quantitation of the** (b) (4) **as potential impurities.**

- **Impurities should be categorized as peptide-related and non-peptide-related impurities.**

- **Regarding the stability protocol, provide data to demonstrate your proposed assay methods are stability indicating.**

- **General USP (XXVII) test methods should be used unless you demonstrate that Ph. Eur. test methods are superior and/or comparable after adequate validation.**

Drug Product:

- **Develop adequate stability-indicating assays to demonstrate that** (b) (4) **is the only degradant product.**

- **Clarify how content uniformity and fill volume are tested.**

- **Consult the Agency regarding Sterility and Microbiology issues related to the drug substance and drug product manufacturing.**

General:

- **Refer to the following guidances:**
    - **Guidance for Industry INDs for Phase 2 and Phase 3 Studies**
    - **Chemistry, Manufacturing, and Controls Information, ICH Q6A and Q6B, etc.**

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/s/

Ryan Barraco
7/23/04 12:24:22 PM

Ramesh Raghavachari
7/23/04 12:55:58 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,214

Jerini AG c/o Target Health Inc.
Attention: Jules Mitchel, Ph.D.
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Mitchel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Icatibant (JE 049) subcutaneous (S.C.).

We also refer to your April 15, 2004, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Icatibant (JE 049) subcutaneous (S.C.) for treatment of hereditary angioedema as a fast track product.

We are granting fast track designation for the following reasons:

1. Hereditary angioedema (HAE) is a serious condition. HAE is an autosomal dominant disorder caused by a deficient or nonfunctional C1 esterase inhibitor (C1-INH) clinically characterized by recurrent and self-limiting local swelling at 3 main sites: subcutaneous tissue, gastrointestinal tract, and larynx. Laryngeal edema is life-threatening and can lead to death in up to 40% of patients. Misdiagnosis of abdominal symptoms of HAE can lead to unnecessary emergency abdominal surgery.

   You propose to evaluate the efficacy and safety of Icatibant in the relief of symptoms resulting from moderate to severe acute cutaneous abdominal edema attacks in patients with HAE. You propose to explore efficacy and safety of Icatibant in patients experiencing laryngeal edema attacks.

2. Currently approved drugs used as continuous prophylaxis of recurrent attacks of HAE in the U.S. include Danocrine (danazol) and Winstrol (stanozolol). No drugs have been approved in the U.S. for treatment of acute attacks of HAE. Preclinical studies suggest that Icatibant may be useful for the treatment of acute attacks of HAE.

Therefore, the drug has a potential to address unmet medical needs and the development program is designed to evaluate this potential.

If you pursue a clinical development program that does not support use of Icatibant (JE 049) subcutaneous (S.C.) for treatment of hereditary angioedema, we will not review the application under the fast track development program.

Also, please consider conducting an additional study to adequately evaluate the efficacy and safety of Icatibant for treatment of acute laryngeal attack of hereditary angioedema.

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at 301-443-8017.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
6/15/04 03:28:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 68,214

Jerini AG
c/o: Target Health Inc.
Attention: Jules Mitchel, Ph.D., President
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Mitchel:

Please refer to the meeting between representatives of your firm and FDA on February 6, 2004. The purpose of the meeting was to discuss how the S.C. formulation will fit into the overall development process and to also discuss Fast Track, Priority Review and Accelerated Approval for (b) (4) S.C formulations.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Ryan Barraco, B.A., B.S.
Consumer Safety Officer
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 6, 2004

TIME: 12:30 PM 2:00 PM

LOCATION: Parklawn Building, 3rd Floor, Conference Room "Chesapeake"

APPLICATION: PIND 68,214
Icatibant (JE 049) (b) (4) S.C.

TYPE OF MEETING: Type B: Pre- IND

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Ryan Barraco

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Dr. Paul Maher	Medical Officer	Orphan Products Division (HF-35)
2. Dr. Robert Justice	Division Director	Division of Gastrointestinal and Coagulation Drug Products (DGCDP) (HFD-180)
3. Dr. Joyce Korvick	Deputy Director	DGCDP (HFD-180)
4. Dr. Jasti Choudary	Supervisory Pharmacologist	DGCDP (HFD-180)
5. Ryan Barraco	Consumer Safety Officer	DGCDP (HFD-180)
6. Dr. Min Lu	Medical Officer	DGCDP (HFD-180)
7. Dr. Kathy Robie-Suh	Hematology Medical Officer Team Leader	DGCDP (HFD-180)
8. Dr. Steven Wilson	Deputy Director	Division of Biometrics II (HFD-715)
9. Dr. Ramesh Raghavachari	Chemist	Division of New Drug Chemistry II (HFD-820)
10. Dr. Tien-Mien Chen	Biopharmaceutist	Division of Pharmaceutical Evaluation II (HFD-870)
11. Dr. Suresh Doddapaneni	Biopharmaceutist, Team Leader	Division of Pharmaceutical Evaluation II (HFD-870)

EXTERNAL CONSTITUENT (Jerini AG) ATTENDEES AND TITLES:

External Attendee	Title	Representing
1. Dr. Jochen Knolle	Head of Research and Development	Jerini AG
(b) (4)		
(b) (4)		
4. Dr. Francisco Bracho	Assistant Professor of Clinical Pediatrics, Georgetown University Hospital, Lombardi Cancer	Principal Investigator
(b) (4)		
6. Dr. Jules T. Mitchel	President	Target Health Inc.
7. Dr. Bernd Rosenkranz	Vice President Clinical Development	Jerini AG

BACKGROUND:

Jerini AG submitted a Meeting Request (MR) on December 8, 2003, received December 11, 2003, for a Pre-IND (PIND) meeting for Icatibant (JE 049) (b) (4) S.C. Jerini AG, a foreign company, appointed Dr. Jules T. Mitchel as their U.S. resident agent in their background package submitted January 5, 2004, received January 8, 2004. The firm submitted eleven questions addressed to the Agency and three protocols for Icatibant. On December 19, 2003, a PIND number (68,214) was established for Icatibant.

The firm requested the Pre-IND meeting to discuss how the S.C. formulation will fit into the overall development process and to also discuss Fast Track, Priority Review and Accelerated Approval for (b) (4) S.C formulations.

MEETING OBJECTIVES:

To reach an agreement with the Agency on the responses to the questions posed in the firm's background package.

DISCUSSION POINTS:

In response to the firm's questions in their background package for the meeting, the following agreements were reached after discussion. The format provides for the firm's questions (1-11), followed by the Agency's responses in bold lettering.

Questions and Responses:

1. Jerini intends to cross reference IND (b) (4) Will FDA require Jerini to submit data already on file for IND (b) (4) or can the data be cross-referenced? This IND is currently inactive.

   Agency Response:

   - **You do not appear to be the sponsor for IND (b) (4) In order to cross-reference that IND, Jerini AG must provide a letter from the sponsor of IND (b) (4) giving right of reference to that IND.**

   - **To support the clinical safety of Icatibant, you should integrate all available safety information for the drug in the presentation of the clinical safety data in the initial submission for the new IND.**

   - **Please submit all the relevant data in the IND.**

2. In order to support the NDA, Jerini intends to submit the following additional toxicology studies:

   - One month IV toxicity study in the dog
   - Fertility study in the male and female rat [SEGMENT I]
   - Pre and post-natal study the rat [SEGMENT III]
   - Completion of the safety pharmacology package with a study on respiratory function

   Agency Response:

   - **The studies are acceptable**

3. It is the intension of Jerini to discuss CMC issues with FDA separately. Is this acceptable?

   Agency Response:

   - **It appears to be acceptable. Please refer to "Guidance for Industry - for the submission of CMC information for Synthetic Peptide Substances" and "Guidance for Industry- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-derived Products."**

   - **Yes, we agree with you that you may request a separate EOPII CMC meeting.**

   - **At the time of IND submission the CMC information must be adequate to support use of the drug in the proposed clinical studies.**

4. Jerini believes that the current data on QTc studies will be adequate. Extensive preclinical and clinical studies have been done to evaluate cardiovascular effects of Icatibant, including QTc prolongation. There has been no evidence for any adverse effects of the drug on cardiovascular function, including repolarization. Jerini intends to continue to adequately monitor patients in all clinical trials. Does the Agency have any comments on this approach?

   Agency Response:

   - **You should submit current data on QTc studies including pre-clinical and clinical studies for review. Appropriate comments will be provided after reviewing the relevant data.**

   - **Refer also to Draft ICH Consensus Guideline: Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.**

5. Jerini would like feedback of the Agency about the proposed design of the pivotal study JE 049 #2103, including sample size and endpoints.

Agency Response:

- **The response rate should be the primary efficacy endpoint. Response should be defined as a clinically meaningful amount of improvement in the symptoms being assessed within a pre-specified amount of time. If time to onset of symptom relief is taken as the primary efficacy endpoint, a pre-specified amount of difference in this endpoint between the treatment groups will be indicated in the protocol and justification provided that this difference is clinically meaningful. An evaluation of durability of response should be made.**

- **"Response" should be as objective as possible and should be defined clearly and completely in the protocol (for each presenting symptom).**

- **Justification for the pre-specified amount of improvement being clinically meaningful should be provided.**

- **Time to onset of symptom relief can be a primary efficacy endpoint. Consider a physician global assessment as a supportive endpoint.**

- **The study should be sized based on the expected difference in primary efficacy endpoint between treatment groups.**

- **Validation of the visual analog scales (VAS) proposed for use in assessing efficacy should be provided. It is not clear that a 20 mm change in VAS score is clinically meaningful.**

- **It is not clear whether the investigator/designee or the patient will mark the VAS. The sponsor states that the patient will mark the VAS.**

- **It is not clear how the response to the question, "Are you confident that your condition is improving?" will be used to further validate the start of symptom relief/expressed relief.**

- **You propose an interim analysis. This may affect the statistical analysis. Details of the interim analysis, e.g. alpha-spending function, need to be specified.**

- **Provide discussion as to how blinding will be maintained.**

- **Adequate safety and bioavailability information must be provided to support the subcutaneous route of administration.**

- **The full study protocol should be submitted for review.**

6. Since there is currently no product on the market to treat acute attacks of hereditary angioedema, Jerini is requesting Fast Track designation. Jerini will also be requesting Priority Review and Accelerated Approval.

Agency Response:

- **Priority review will be decided at the filing meeting after an NDA is submitted and will depend on the data.**

- **Submit a request for Fast Track Designation. See Guidance for Industry: Fast Track Drug Development Program-Designation, Development, and Application Review.**

- **You appear to misunderstand Accelerated Approval. It applies to the use of surrogate endpoints or restricted distribution. (See 21 CFR 314 Subpart H)**

7. Jerini is currently planning to utilize the absolute bioavailability study, JE 049 #1102, the open-label study being performed in Europe, JE 049 #2101 and the Pivotal Protocol JE 049 #2103 to support the clinical requirements for the NDA submission. Jerini believes this is adequate for marketing approval. Does the agency agree?

Agency Response:

No.

- **Generally two adequate and well-controlled studies are required for a new indication. See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products.**

- **The proof-of-concept study (#2101) is ongoing. The study is open-label in design and it is not clear at this time how useful it will be with regard to efficacy, dose-selection and/or safety.**

- **It is not clear that the clinical safety database in the target population (patients with hereditary angioedema) will be adequate to support approval. Safety data from other studies that have been conducted should be included.**

- **It is unclear if there is adequate clinical pharmacology data to support the proposed indication.**

8. Alternatively, Jerini is considering submitting an NDA based of the ongoing open-label study, JE 049 #2101, which will have IV and SC treatment arms, and the absolute bioavailability study, JE 049 #1102, in support of the request for Priority Review and Accelerated Approval strategic approaches. In this scenario, Jerini will commit to perform Protocol JE 049 #2103 as part of a post-marketing commitment. Is this acceptable to the agency?

Agency Response:

No.

- **The ongoing study JE 049 #2101 is a proof-of-concept study.**

- **See response to #6.**

9. Since Icatibant has received Orphan Drug Designation, Jerini wants to confirm that there will be no user fee required.

Agency Response:

Yes, the user fee is waived. However, other product development and post-marketing fees (the establishment fee and the product fee) are not waived.

10. Is a Special Protocol Assessment Request needed in addition to agreements made at the pre-IND meeting?

Agency Response:

- **You should submit the initial IND with a full study protocol for review. You also may submit a Special Protocol Assessment Request for the pivotal trial protocol with questions for review and response.**

11. Does the division recommend that Jerini submit a Targeted Product Information document with the IND?

Agency Response:

Yes.

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

/s/

Ryan Barraco
2/20/04 09:18:22 AM

Kathy Robie-Suh
2/23/04 11:17:51 AM