CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021825Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021825 SUPPL # N/A HFD # 161

Trade Name Ferriprox

Generic Name Deferiprone

Applicant Name ApoPharma, Inc.

Approval Date, If Known October 14, 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?

Five (5) years exclusivity for a new chemical entity; Seven (7) years exclusivity for 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: Mara Miller, M.A.
Title: Regulatory Project Manager
Date: October 11, 2011

Name of Office/Division Director signing form: Ann Farrell, M.D.,
Title: Acting Division Director

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

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

/s/

MARA B MILLER
10/11/2011

ANN T FARRELL
10/14/2011

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

NDA/BLA#: 21-825 Supplement Number: N/A NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Medical Imaging and Hematology Products. PDUFA Goal Date: November 30, 2009 Stamp Date: 1/30/2009

Proprietary Name: Ferriprox

Established/Generic Name: deferiprone

Dosage Form: 500 mg film-coated tablets

Applicant/Sponsor: ApoPharma, Inc.

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): 2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: the treatment of iron overload in patients with transfusion-dependent thalassemia.

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[Δ]
☐	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.*)

Δ 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: the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

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 failedΔ
☐	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.*)

Δ 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)

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

/s/

Hyon Z Lee

3/2/2009 11:21:28 AM

DEBARMENT CERTIFICATION

We, the undersigned, hereby certify that ApoPharma Inc. did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application.

09 March 2009

John Connelly, Ph.D. Date
Vice President, Regulatory Affairs and Non-Clinical Research
ApoPharma, Inc.

09 March 2009

Lynda Sutton, B.S. Date
Chief Regulatory Officer
Cato Research Ltd.

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Friday, October 14, 2011 10:29 AM
To: 'Evan Richardson'
Cc: 'Lynda Sutton'
Subject: NDA 021825 Medication Guide

Attachments: MedGuide_NDA21825_FINAL_14OCT11.doc

Hello Evan,

Please confirm via email that ApoPharma agrees to the following change in the Medication Guide on page 1:

It is not known if FERRIPROX tablets (b) (4) are safe and effective:

- to treat iron overload due to blood transfusions in people with any other type of anemia that is long lasting (chronic)
- in children

Thank you,
Mara

MedGuide_NDA218
25_FINAL_14OCT1..

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
10/14/2011

Miller, Mara Bauman

From: Holmes, Loretta
Sent: Thursday, October 13, 2011 4:50 PM
To: Miller, Mara Bauman
Cc: Chan, Irene Z.
Subject: RE: Ferriprox container label

Hi Mara,
The revised container label is acceptable.
Thanks,
Loretta

From: Holmes, Loretta
Sent: Thursday, October 13, 2011 11:40 AM
To: Miller, Mara Bauman
Cc: Chan, Irene Z.
Subject: Ferriprox container label

Hi Mara,
We have the following comment regarding the revised container label submitted on October 11, 2011.

> Relocate the Medication Guide (MG) statement to the principal display panel and position it below the strength. If additional space is needed to accommodate the MG statement, consider decreasing the size of the net quantity statement.

Thanks,
Loretta

Loretta Holmes, BSN, PharmD
Safety Evaluator
Food and Drug Administration
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Division of Medication Error Prevention and Analysis (DMEPA)
10903 New Hampshire Avenue
Building 22, Room 4445, Mail Drop 4447
Silver Spring MD 20993-0002
Office: 301-796-0170 Fax: 301-796-9865
Email: loretta.holmes@fda.hhs.gov

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

---

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

/s/

MARA B MILLER
10/14/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Thursday, October 13, 2011 11:57 AM
To: 'Evan Richardson'
Cc: Lynda Sutton
Subject: NDA 021825 Container Label

Hello Evan,

Regarding the revised container label emailed on October 11, 2011, we have the following comment:

Relocate the Medication Guide (MG) statement to the principal display panel and position it below the strength. If additional space is needed to accommodate the MG statement, consider decreasing the size of the net quantity statement.

Thank you,
Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

---

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

/s/

MARA B MILLER
10/14/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Wednesday, October 12, 2011 4:11 PM
To: 'Evan Richardson'; Lynda Sutton
Subject: Information Request- PMRs/PMCs NDA 021825

Attachments: List_PMR_PMC_NDA021825.pdf

Hello Evan and Lynda,

Attached is the full list of PMRs and PMCs for Ferriprox, NDA 021825. Please note, for the PMR regarding a registry, we need ApoPharma to provide a month and year for the timelines.

Please confirm that ApoPharma agrees to these PMRs and PMCs. A confirmatory response should be sent via email and followed by an official submission titled "Response to Information Request- PMR and PMC Agreement." Please send the response as soon as possible on the morning of Thursday October 13, 2011.

Thank you,
Mara

List_PMR_PMC_ND
A021825.pdf (19...

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

Summary of Post Marketing Requirements (PMR) and Commitments for Ferriprox with Estimated Timelines

PMRs under Accelerated Approval (Subpart H)

1. Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Submit the protocol for review and concurrence prior to commencing. The trial will enroll a sufficient number of patients with sickle cell disease as described above, to provide sufficient evidence to assess the efficacy and safety in the sickle cell disease population described. The trial may enroll patients with other conditions who have developed transfusional iron overload. The trial will stratify for hematologic diagnosis for the randomization. The primary and secondary endpoints will measure changes in cardiac iron concentration and liver iron concentration.

Final Protocol Submission: February 2012
Trial Completion: January 2016
Final Report Submission: July 2016

PMRs under FDAAA

1. Conduct a clinical trial per ICH E14 to assess the potential for deferiprone to prolong the QT interval. Submit the protocol for IRT review and concurrence prior to commencing.

Final Protocol Submission:	January 2012
Trial Completion:	July 2013
Final Report Submission:	December 2013

2. Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment. This pharmacokinetic trial should be conducted in a population with mild to severe hepatic insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that are representative of the indicated population (e.g., age, weight, gender, race). Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	September 2012
Trial Completion:	February 2014
Final Report Submission:	July 2014

3. Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with renal impairment. This pharmacokinetic trial should be conducted in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that represent the indicated population (e.g., age, weight, gender, race) to the extent possible. Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	September 2012
Trial Completion:	February 2014
Final Report Submission:	July 2014

4. (b) (4)

5. Submit a protocol to establish a registry and describe procedures to provide enhanced pharmacovigilance for agranulocytosis. Procedures are to include: Plan to have marketing materials inform and encourage clinicians to report agranulocytosis events to the sponsor; sponsor will monitor all reported cases and will seek additional information to characterize the demographics, recent prior blood counts, concomitant medications, co-existing conditions, duration of drug exposure prior to onset, outcomes of the event, and other factors that may help to characterize the agranulocytosis event. Sponsor also will institute procedures to obtain blood samples or reported cases to store for later analysis of possible genetic underlying factors that may predict the risk of agranulocytosis. Submit interim reports annually describing the above results. Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	6 months following approval
Trial Completion:	7 years following approval
Final Report Submission:	7.5 years following approval

(b) (4)

Post Marketing Commitment

1. Conduct in vitro studies to determine the effect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the

metabolism of deferiprone. The results of the in vitro evaluations will determine the need for additional in vivo drug interaction trials.

Final Protocol Submission:	January 2012
Trial Completion:	July 2013
Final Report Submission:	October 2013

2. To submit results of the "Tanner" trial comparing the effects of deferoxamine alone to the combination of deferoxamine plus Deferiprone in patients with thalassemia major, reported in the journal "Circulation" in 2007. Submit the clinical trial report and complete, raw datasets and analysis programs.

   Final Protocol Submission: March 2012
   Trial Completion: July 2012
   Final Report Submission: October 2012

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

/s/

MARA B MILLER
10/12/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Tuesday, October 11, 2011 9:45 AM
To: 'Evan Richardson'
Cc: Lynda Sutton
Subject: RE: Ferriprox PMR/PMC

Good Morning,

Regarding PMR #1- *Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents*- please confirm that ApoPharma agrees that the primary and secondary endpoints would involve assessment of the change in cardiac iron and liver iron.

Thank you,
Mara

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Monday, October 10, 2011 2:18 PM
To: Miller, Mara Bauman
Cc: Lynda Sutton
Subject: Re: Ferriprox PMR/PMC

Hi Mara,

Please find attached below ApoPharma's latest response to the PMRs/PMCs. Per your email on Friday afternoon, we'll ask ApoPharma to wait until you've confirmed your agreement with these responses before officially submitting them. We'll be prepared to do this on Tuesday.

Please let me know if you have any questions.

Thanks,
Evan

(See attached file: 11-1008l PMR PMC resp due 10 Oct .pdf)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

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

/s/

MARA B MILLER
10/11/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Friday, October 07, 2011 4:47 PM
To: Lynda Sutton; 'Evan Richardson'
Subject: NDA 021825 Information Request

Hello Lynda and Evan,

A revised Ferriprox container label was submitted on June 14, 2011. However, since that time, it has been determined that Ferriprox will require a Medication Guide. The container label submitted on June 14, 2011 does not have a Medication Guide statement. Therefore, we recommend the following language be placed on the principal display panel of the container label in bold font:

"**Attention Pharmacist: Dispense the accompanying Medication Guide to each patient**"

Pleases respond by respond by 12:00 PM Wednesday, October 12, 2011.

Thank you,

Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
10/11/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Friday, October 07, 2011 10:37 AM
To: 'Evan Richardson'
Cc: Lynda Sutton
Subject: RE: NDA 021825 - PMR and Labeling Responses

Hello Evan and Lynda,

Thank you for the responses.

Regarding Section 17 of the label, the Medication Guide is not a subsection and is not numbered as a subsection. The medication guide is just appended to the of the Patient Counseling Information. Therefore, Section 17 numbering will not be changed. Please let me know if you have any questions.

Thank you,
Mara

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Friday, October 07, 2011 10:00 AM
To: Miller, Mara Bauman
Cc: Lynda Sutton
Subject: NDA 021825 - PMR and Labeling Responses

Hi Mara,

In follow up to yesterday's teleconferences, please find attached below ApoPharma's responses to the PMRs and to the Agency's labeling comments.

Please let me know if you have any questions.

Thanks,
Evan

(See attached file: Ferriprox label response 07 Oct.pdf)(See attached file: Response to PMR 06 Oct final.pdf)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

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

/s/

MARA B MILLER
10/11/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Thursday, October 06, 2011 3:04 PM
To: 'Evan Richardson'; 'Lynda Sutton'
Subject: RE: Ferriprox Label - Section 13.1

Hello Evan and Lynda,

The team has reviewed ApoPharma's response to question #2 and has the following counterproposal (black text is original, red text is the new text):

Carcinogenicity studies have not been conducted with deferiprone. However, in view of the genotoxicity results and the findings of mammary gland hyperplasia and mammary gland tumors in rats treated with deferiprone in the 52-week toxicology study, (b) (4)

Thank you,
Mara

"Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

"Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>	To	'"Lynda Sutton"' <lsutton@cato.com>, '"Evan Richardson"' <erichard@cato.com>
10/05/2011 05:13 PM	cc	
	Subject	Ferriprox Label

Hi Lynda,

Can you ask ApoPharma the following questions:

1. Do they think they could get the data from the Tanner et. al. paper published in Circulation in 2007 entitled "A Randomized Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy with Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance".

2. Regarding the Comment in label in Section 13.1- Note to Applicant: This information must be kept in the label. We will reevaluate the data once you submit the results of carcinogenicity studies.

(b) (4) - We are assuming ApoPharma is not agreeing to keep this in the label, correct?

Thanks,
Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
10/06/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Wednesday, October 05, 2011 5:13 PM
To: 'Lynda Sutton'; 'Evan Richardson'
Subject: Ferriprox Label

Hi Lynda,

Can you ask ApoPharma the following questions:

1. Do they think they could get the data from the Tanner et. al. paper published in Circulation in 2007 entitled "A Randomized Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy with Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance".

2. Regarding the Comment in label in Section 13.1- Note to Applicant: This information must be kept in the label. We will reevaluate the data once you submit the results of carcinogenicity studies.

(b) (4)

- We are assuming ApoPharma is not agreeing to keep this in the label, correct?

Thanks,
Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
10/06/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Monday, October 03, 2011 5:12 PM
To: Lynda Sutton; 'Evan Richardson'
Subject: NDA 021825- Label

Importance: High

Attachments: NDA021825_Label_FDA_03OCT11.doc

Hello,

Attached is the label with FDA comments. Were we agree, we have accepted the text. Where we did not agree, we deleted added text and commented on many items. There is some revised text as well.

Please provide comments by COB on Tuesday October 4 so that we have time to review and have a t-con if needed.

Thanks,
Mara

NDA021825_Label_
FDA_03OCT11.do...

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

---

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

/s/

MARA B MILLER
10/14/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Monday, October 03, 2011 9:13 AM
To: 'Evan Richardson'; Lynda Sutton
Subject: NDA 021825 Post Marketing Requirements

Attachments: List_PMR_PMC_NDA021825.doc

Good Morning Lynda and Evan,

Attached is the list of the FDA's PMRs/PMCs for NDA 021825. The Division is open to some "enhancements" and tweaks that ApoPharma may feel will help facilitate things, but major parts of these PMR/PMC concepts are generally not negotiable.

Please provide dates, in the form of month/year in which ApoPharma expect's to complete each segment required for each item. The term "final protocol submission" means the official submission of a final version following concurrence by FDA on the protocol.

Please provide comments by COB on Tuesday October 6, 2011.

Thank you,
Mara

List_PMR_PMC_ND
A021825.doc (45...

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

Summary of Post Marketing Requirements (PMR) and Commitments for Ferriprox with Estimated Timelines

PMRs under Accelerated Approval (Subpart H)

1. Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	January 2012
Trial Completion:	January 2014
Final Report Submission:	July 2014

PMRs under FDAAA

1. Conduct a clinical trial per ICH E14 to assess the potential for deferiprone to prolong the QT interval. Submit the protocol for IRT review and concurrence prior to commencing.

Final Protocol Submission:	January 2012
Trial Completion:	January 2013
Final Report Submission:	July 2013

2. Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment. This pharmacokinetic trial should be conducted in a population with mild to severe hepatic insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that are representative of the indicated population (e.g., age, weight, gender, race). Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	January 2012
Trial Completion:	July 2013
Final Report Submission:	October 2013

3. Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with renal impairment. This pharmacokinetic trial should be conducted in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that represent the indicated population (e.g., age, weight, gender, race) to the extent possible. Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	January 2012
Trial Completion:	July 2013
Final Report Submission:	October 2013

4. (b) (4)

5. Submit a protocol to establish a registry and describe procedures to provide enhanced pharmacovigilance for agranulocytosis. Procedures are to include: Plan to have marketing materials inform and encourage clinicians to report agranulocytosis events to the sponsor; sponsor will monitor all reported cases and will seek additional information to characterize the demographics, recent prior blood counts, concomitant medications, co-existing conditions, duration of drug exposure prior to onset, outcomes of the event, and other factors that may help to characterize the agranulocytosis event. Sponsor also will institute procedures to obtain blood samples or reported cases to store for later analysis of possible genetic underlying factors that may predict the risk of agranulocytosis. Submit interim reports annually describing the above results. Submit the protocol for review and concurrence prior to commencing.

Final Protocol Submission:	6 months following approval
Trial Completion:	8.5 years following approval
Final Report Submission:	9 years following approval

Post Marketing Commitment

1. Conduct in vitro studies to determine the effect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone. The results of the in vitro evaluations will determine the need for additional in vivo drug interaction trials.

Final Protocol Submission:	January 2012
Trial Completion:	July 2013
Final Report Submission:	October 2013

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

/s/

MARA B MILLER
10/12/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Friday, September 30, 2011 10:30 AM
To: 'Evan Richardson'; Lynda Sutton
Subject: NDA 021825 Information Request

Importance: High

Hello Evan and Lynda,

We have the following information request for NDA 021825, Ferriprox. Please respond by Monday October 3, 2011 5:00 PM.

1. Clarify how you will ensure an adequate number of Medication Guides are available to permit the authorized dispensers to provide one to each patient.

2. We note the container label is an Expanded Content Label (ECL). Please submit the contents of the ECL.

Thank you,

Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
09/30/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Monday, September 26, 2011 11:51 AM
To: Lynda Sutton; 'Evan Richardson'
Subject: NDA 021825 Draft Label

Importance: High

Attachments: label_NDA21825Ferriprox_FinalDraft_26Sept11.doc

Hello Lynda and Evan,

Attached is the Ferriprox Label based on FDA review. In order to facilitate negotiations, please return initial ApoPharma comments on Wednesday September 28, 2011.

Where ApoPharma agrees with the label, please accept the track change. Where ApoPharma does not agree with the label, please provide comments/proposed language.

Thank you,
Mara

label_NDA21825Fer
riprox_FinalD...

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

---

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

/s/

MARA B MILLER
10/12/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Friday, September 23, 2011 8:38 AM
To: 'Evan Richardson'
Cc: Lynda Sutton; Lambert, Tu-Van
Subject: NDA 021825 Information Request

Importance: High

Dear Mr. Richardson,

Based on the evaluation of the dissolution information/data provided on your September 22nd response, Biopharmaceutics agrees with your conclusion that the provided dissolution data support an acceptance criterion of Q= (b) (4) in 45 minutes for your product. Therefore, we recommend that Q= (b) (4) in 45 minutes be set as the final Acceptance criterion for your product. Please provide your concurrence and an updated specification sheet for your "Drug Product Release Specifications", including the revised criterion of Q= (b) (4) at 45 minutes for the dissolution test. Provide this information by 4:00 PM Friday September 23, 2011.

Thank you,

Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
09/23/2011

MEMORANDUM OF MEETING

MEETING DATE: September 20, 2011
TIME: 4:00 PM – 4:30 PM
LOCATION: White Oak 22, 2376- Teleconference
APPLICATION: NDA 021825
DRUG NAME: Ferriprox® (Deferiprone)
TYPE OF MEETING: Discussion of Application Review Status

MEETING CHAIR: Ann Farrell, M.D.

MEETING RECORDER: Mara Miller, M.A.

FDA ATTENDEES:

Division of Hematology Products
Ann Farrell, M.D., Acting Division Director
Kathy Robie Suh, M.D., Ph.D., Clinical Team Lead
George Shashaty, M.D., Clinical Reviewer
Mara Miller, M.A., Regulatory Project Manager

Office of New Drug Quality Assessment
Sarah Pope Miksinski, Ph.D., Branch Chief
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader
Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

ApoPharma
Michael Spino, President
Fernando Tricta, VP, Medical Affairs
John Connelly, VP, Regulatory and Nonclinical
Lopa Bandyopadhyay, Manager, Regulatory Affairs
Anna Rozova, Director, Medical Safety
Carolina Fredette, Principal Scientist, Clinical Research

Cato Research
Lynda Sutton
Evan Richardson
Allison Lehtinen

BACKGROUND:

The Agency held a teleconference with ApoPharma to discuss outstanding action items for the review of NDA 021825. The Agency identified some CMC and Biopharmaceutics issues that require immediate resolution to allow sufficient time for review of the data prior to the PDUFA date of October 14, 2011. On September 20, 2011, ApoPharma submitted a partial response to a pending information request from August 10, 2011. ApoPharma stated that a complete response will be provided by September 30, 3011. The Agency and ApoPharma discussed the remaining deficiencies and timelines for resolution.

DISCUSSION POINTS:

- The Agency mentioned that the information provided in the Applicant's response to the Biopharmaceutics deficiency was adequate. The Agency indicated that the newly submitted dissolution data support their recommended dissolution acceptance criterion of (b) (4) and asked for the Applicant's confirmation. ApoPharma responded that they consider that (b) (4) is an appropriate specification for their product and they will submit a proposal with a detailed rationale for this proposal.
- Discussion of CMC Deficiency #1: The response stated that ApoPharma would not withdraw the Apotex Pharmachem site and planned to submit the validation data at the end of September. The Agency stated that this proposed path will not allow sufficient time to review the validation data prior to the PDUFA date. The Agency confirmed that the Applicant could withdraw the site from the application, and that it would be feasible for the Applicant to submit this site via a post-approval supplement. ApoPharma agreed to withdraw Apotex Pharmachem from the application.
- Discussion of CMC Deficiency #2a: The Agency stated that if approved, the Action Letter will include the expiration date. Confirmation of an expiration dating period is not provided to applicants prior to an action.
- Discussion of CMC Deficiency #2b: The response stated that ApoPharma proposes to add Apotex Research Pvt. Ltd. (India) as a site for stability testing. The Agency acknowledged the clarification and stated that any new site added to the application would need to be evaluated. The Agency confirmed that there is not sufficient time to evaluate a new site in this cycle. The Agency stated that the Applicant has the option of withdrawing the site and that the site could then be submitted as a post-approval supplement. ApoPharma agreed with this approach.
- Discussion of CMC Deficiency #3: ApoPharma did not provide a response to deficiency #3 as it is still under discussion. The Agency stated this information must be provided by close of business on September 22, 2011.
- The Agency summarized other pending review items:
    - The status of a current facility inspection is pending.
    - The Division expects to send the label this week.
    - The Division is discussing the post-market confirmatory trial and expects to schedule discussions with ApoPharma.

ACTION ITEMS:

- ApoPharma will respond to all deficiencies by close of business on September 22, 2011.
- ApoPharma will provide a proposal and rationale for the counter-proposed dissolution acceptance criterion.
- ApoPharma will withdraw the Apotex Pharmachem site from this application and will submit the site as a post-approval supplement.
- ApoPharma will submit the Apotex Research Pvt. Ltd. (India) site as a post-approval supplement.
- ApoPharma will provide a full response to CMC deficiency #3.

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

/s/

MARA B MILLER
09/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Office of Clinical Pharmacology Division of Clinical Pharmacology 5 Tracking/Action Sheet for Formal/Informal Consults

From: Joseph A. Grillo, Pharm.D.	To: DOCUMENT ROOM (LOG-IN & LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission

Date: 9/20/11	IND No.: Serial No.: SDN:	NDA No. 21-825 Serial No.: SDN:	Document ID: N	Date of Document: 9/13/11

Name of Drug Ferriprox (deferiprone) Tablets	Priority Consideration ☐ Yes ☐ No ☒ N/A	DARRTS Categories/Subcategories: CONSULT

Name of Sponsor: ApoPharma USA

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY RELATED ISSUE

☐ PRE-IND	☒ BA/BE STUDIES	☐ IN-VIVO WAIVER REQUEST
☐ ORIGINAL IND	☐ ORGAN IMPAIRMENT STUDIES	☒ CMC RELATED
☐ RESPONSE TO COMMENTS	☐ QT	☐ CORRESPONDENCE
☐ RESPONSE TO HOLD/REACTIVATION	☒ FORMULATION	☐ IN-VITRO METABOLISM
☐ NEW PROTOCOL	☐ PK/PD- POPPK ISSUES	☐ ADVERSE REACTION REPORT
☐ PROTOCOL CHANGE	☐ PHASE IV RELATED	☐ ANNUAL REPORTS
☐ PHASE 2 PROTOCOL	☐ DOSING REGIMEN CONSULT	☐ INVESTIGATORS BROCHURE
☐ PHASE 3 PROTOCOL	☒ PEDIATRICS	☒ OTHER *(SPECIFY BELOW):*
☐ SPECIAL PROTOCOL ASSESMENT	☐ MEETING PACKAGE ( )	Consult

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)	☐ Comments communicated in meeting/Telecon.	☐ See submission cover letter
	see meeting minutes dated: [ ]	☐ OTHER *(SPECIFY BELOW)*: [ ]

******Pre-decisional Agency Information******

This is in response to a 9/13/11 consult from the Division of Hematology Products (DHP) requesting a review of the bioavailability of the deferiprone solution formulation used in ApoPharma's trial LA30-0307 compared to the bioavailability of the to-be-marketed tablets. The Division would like to use this information to determine if the data obtained in Trial LA30-0307 can be used (b) (4) .

Background: The applicant is not planning to market a solution formulation of Ferriprox®; however, BA/BE related information regarding a deferiprone solution formulation was submitted with the original application on 3/28/2007 in trials LA20-BA (An Open Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox) and Deferiprone Solution Under Fasting and Fed Conditions) and Trial LA21-BE (Randomized, Open Label, Comparative, Two-Way Crossover Bioavailability Study Of Deferiprone Oral Solution And Ferriprox (Deferiprone) Tablets Under Fasting Conditions). The deferiprone solution formulation used in each of these trials was different (Table 1). Since the applicant did not specify the deferiprone solution formulation used in trial LA30-0307, DHP sent an information request to the applicant on 9/711 requesting a table comparing the composition of the liquid formulation used in studies LA20-BA, LA21-BE and LA30-0307. The applicant responded on 9/8/11 with the following information:

Table 1: Composition of deferiprone oral solution formulations used in trials LA20-BA, LA21-BE and LA30-0307

Ingredient	Composition (g/L)		
	Formulation used in LA20-BA	Formulation used in LA21-BE	Formulation used in LA30-0307
Deferiprone (In-house standard)	100.00	100.00	100.00
(b) (4)			

(b) (4)

Based on the above information it appears the deferiprone solution formulation used in ApoPharma's trial LA30-0307 was the same as that used in the trial LA21-BE. This trial was not formally reviewed by OCP as part of the original application because the applicant did not plan to market the deferiprone solution formulation. However, we are providing a review here specifically to address the question posed in this consult from DHP.

Review of Trial LA21-BE

Trial LA21-BE was an open label, single-dose, randomized, two-way crossover comparative bioavailability trial performed on 42 healthy adult subjects. An oral dose of 1500 mg of deferiprone either in the tablet form (3 × 500 mg Ferriprox tablets) or in the form of solution (1 × 15 mL of 100 mg/mL

solution) was administered under fasting conditions. The single doses were separated by a washout period of seven days. Blood samples for PK were collected at Hour 0 (pre-dose) and at 5, 10, 20, 30, 45 minutes, and 1, 1.33, 1.66, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours postdose. Descriptive statistics of all PK parameters were provided for deferiprone. The evaluation of relative bioavailability was tested for AUC0-t, AUCinf and Cmax by constructing the 90% confidence interval (CI) for the ratio of the treatment LSM of interest. A predetermined equivalence range of 80-125% was set by the applicant.

The general design, PK sampling scheme, assay, and data analysis used in trial LA21-BE was similar to that used in the food effect portion of trial LA20-BA that was perviously deemed acceptable by OCP (see the 3/27/2008 and 09/24/2009 reviews by Dr. Hepp). The LA21-BE trial population consisted of 42 healthy adult subjects (29 males and 13 females) with a mean age of 38 years (range of 19 – 55 years). The reported deferiprone exposure in trial LA21-BE was similar between the tablet and solution formulations (see Table 2).

Table 2: Summary of pharmacokinetic results - Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a solution and a tablet under fasting conditions

Parameter	Solution (A)	Tablet (B)
AUC_{0-t} * (µg·h/mL)	48.2 (22.6) n = 41	48.0 (23.3) n = 41
AUC_{inf} * (µg·h/mL)	49.3 (22.9) n = 41	49.2 (23.4) n = 41
C_{max} (µg/mL)*	18.9 (30.8) n = 41	19.2 (36.2) n = 41
t_{max} (h)	0.805 (66.6)	0.911 (50.5)
kel (1/h)	0.412 (13.8)	0.410 (14.3)
Half-life (h)	1.71 (13.4)	1.72 (13.3)

n: number of observations

*Geometric means are presented for these parameters.

In addition, the 80-125% equivalence criteria were met for all the exposure parameter studied (Table 3). The non-parametric 90% confidence interval for the median of the test – reference difference (formulation effect) for Tmax was [-0.292; 0.000]. Therefore, the reviewer finds the exposures resulting from administration of the same dose of each of the two formulations equivalent.

Table 3: Ratios of LSM % (90% Confidence Intervals) for deferiprone in serum

Parameter	Deferiprone Solution (A) vs Tablet (B)
AUC_{0-t}	100.6% (98.0% – 103.4%)
AUC_{inf}	100.4% (97.7% – 103.1%)
C_{max}	98.3% (88.9% – 108.7%)

Recommendation:

We reviewed the trial LA21-BE from a clinical pharmacology perspective and find that the deferiprone solution formulation used in this trial is bioequivalent to the Ferriprox tablet formulation. The same deferiprone solution formulation was used in trial LA30-0307. We defer to CMC regarding the integrity of the deferiprone solution batches used in these studies.

Signatures:

Joseph A. Grillo, Pharm.D. Reviewer Division of Clinical Pharmacology 5	Julie Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **MB Miller;** MTL - **K Robie Suh**; MO - **G Shashaty**
DCP-5: Reviewer - **J Grillo;** TL - **J Bullock;** Deputy DD - **B Booth;** DD - **A Rahman**

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

/s/

JOSEPH A GRILLO
09/20/2011

JULIE M BULLOCK
09/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21825 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Cato Research
Attention: Lynda Sutton
US Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) 500 mg Film-Coated Tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)[1]. The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

[1] These violations include studies conducted by (b) (4)

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by (b) (4) during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Division Director (Acting)
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
09/20/2011

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE, Sue Kang**			FROM: Mara Miller, DHP 6-0683	
DATE 9/20/11	IND NO.	NDA NO. 021825	TYPE OF DOCUMENT Medication Guide	DATE OF DOCUMENT Pending
NAME OF DRUG Ferriprox	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Iron Chelator	DESIRED COMPLETION DATE Within 2 weeks from receipt

NAME OF FIRM: ApoPharma

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
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

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

DHP requests a DRISK review of the Patient Labeling (MedGuide) for Ferriprox, NDA 021825. The MedGuide and Label will be sent upon receipt from the applicant.

SIGNATURE OF REQUESTER Mara Miller	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

MARA B MILLER
09/20/2011

Lambert, Tu-Van

From: Lambert, Tu-Van
Sent: Monday, September 19, 2011 10:31 AM
To: 'Evan Richardson'
Cc: Miller, Mara Bauman
Subject: NDA 021825 Biopharmaceutics Information Request

Hi Evan,

As I stated in our phone call earlier today, please find in this email the Biopharmaceutics information request for your ApoPharma application.

Your proposed dissolution method as shown below has been accepted:

Apparatus: USP Apparatus II (Paddle)
Rotation Speed: 50 rpm
Medium: 1,000 mL of 0.1 N HCl at 37ºC

However, after a further evaluation on the dissolution profiles/data we consider that the previously agreed dissolution value needs further revision since (b) (4) of the drug is dissolved in (b) (4). Please revise the dissolution acceptance criterion as follows:

Change from (b) (4)
to (b) (4)

Provide an updated specification sheet for your product including the revised criterion for the dissolution test.

If needed the CMC Biopharmaceutics team is available for further discussion if you have any questions. We also patiently await your response to our 8/10/2011 IR letter.

Please confirm that you have received this email, and let me know if you have any questions.

Thank you,

Tu-Van Le Lambert
Product Quality Regulatory Project Manager
ONDQA/OPS/CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 21, Room 2625
Silver Spring, MD 20993
Phone: (301) 796-4246
Fax: (301) 796-9748

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

/s/

TU-VAN L LAMBERT
09/19/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Friday, September 16, 2011 1:59 PM
To: 'Evan Richardson'; Lynda Sutton
Subject: NDA 021825 Information Request

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

We are reviewing your submission and have the following information request. We request a prompt written response by in order to continue our evaluation of your NDA.

1. From your world-wide post-marketing sales/distribution data, published literature and any other sources, please provide any information that may inform as to underlying disease (e.g., hemoglobinopathy type, etc.) in patients who may be receiving the deferiprone.

If you have any questions, call me at (301) 796-0683.

Sincerely,

Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
09/16/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Office of Clinical Pharmacology/ Joe Grillo	Mara Miller, OODP/DHP, 6-0683

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/12/11		021825	Response to IR	9/8/11

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ferriprox (deferiprone)	P	Iron Chelator	9/16/11

NAME OF FIRM: ApoPharma, 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: The Division requests review of the bioavailability of the Ferriprox pediatric liquid formulation used in ApoPharma's Study LA30-0307 compared to the bioavailability of the to-be-marketed tablets. The Division would like to use this information to determine if the data obtained in Study LA30-0307 can be used (b) (4)

MO: George Shashaty
RPM: Mara Miller

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Mara Miller	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

MARA B MILLER
09/13/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Thursday, September 08, 2011 4:27 PM
To: 'Evan Richardson'
Cc: 'Lynda Sutton'
Subject: Information Request, NDA 021825
Importance: High

Hello Evan,

Regarding the response received September 2011 regarding the the information request sent September 6, 2011, we have the following information request.

1. On page one of the response the sponsor states: *" The report was included in the Integrated Safety Summary (**14.2.3.1.1.1 Case 2007AP000570 – Hepatic cirrhosis)** "* Please identify the submission date and location for the cited case.

Thank you,
Mara

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Wednesday, September 07, 2011 7:39 PM
To: Miller, Mara Bauman
Cc: Lynda Sutton; Allison Lehtinen
Subject: Fw: Response to today's information request

Hi Mara,

Please find attached below our response to today's information request. We apologize for providing it later than requested.

Please note that the literature reerence is also provided for your convenience only - it has previosly been submitted to the NDA.

We will submit this response to the NDA in the next few days - we're trying to batch the submission of the responses for efficiency.

Please let me know if you have any questions.

Thanks,
Evan

_____
Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286

Fax: 919.361.2290
erichard@cato.com

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

/s/

MARA B MILLER
09/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

1. Please perform the primary efficacy analysis for LA36 excluding both
   - patients from LA01 and LA03 and
   - patients who received both deferoxamine and deferiprone during the study.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
09/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter. We also refer to your August 22, 2011 response to our August 15, 2011 information request.

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

1. For patients enrolled in LA36 for the primary efficacy evaluation, how many had prior therapy with deferoxamine, how many with deferasirox and how many with both deferasirox and deferoxamine? The Division has been unable to discern the numbers of patients with the different prior treatments from the databases submitted.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
09/08/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Wednesday, September 07, 2011 5:22 PM
To: 'Evan Richardson'; 'Lynda Sutton'
Subject: NDA 021825 Information Request

Dear Ms. Sutton,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

1. For LA36-0310 please provide an analysis of the primary efficacy endpoint excluding both patients who took the liquid formulation (not submitted as to be marketed formulation in the NDA) and patients who received deferoxamine and deferiprone concurrently.

2. Provide a table comparing the composition of the liquid formulation used in studies LA20-BA, LA21-BE and LA30-0307.

3. Provide the following information for study LA30-0307
    - Drug product lots used for the study
    - For each product lot provide
        - API supplier
        - Product formulation
        - Product batch size
        - Test results
        - Any other available information

If you have any questions, call me at (301) 796-0683.

Sincerely,

Mara Miller

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

APPEARS THIS WAY ON ORIGINAL

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

/s/

MARA B MILLER
09/08/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Wednesday, September 07, 2011 10:30 AM
To: 'Allison Lehtinen'; 'Evan Richardson'
Cc: 'Lynda Sutton'
Subject: RE: NDA 021825 Information Request

Good Morning,

In addition to the information requested in the letter, please also indicate the total number of patients in the database that were evaluable for this finding.

Thank you,
Mara

From: Miller, Mara Bauman
Sent: Wednesday, September 07, 2011 10:25 AM
To: 'Allison Lehtinen'; Evan Richardson
Cc: 'Lynda Sutton'
Subject: NDA 021825 Information Request
Importance: High

Good Morning,

Attached is an information request for NDA 021825. Please provide a response via email by 4:30 PM today.

Thank you,
Mara

<< File: Information Request _07SEPT11.pdf >>

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
09/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

For your deferiprone safety database please provide the number and a listing of patients who experienced or had hepatic fibrosis:

1) at baseline (i.e., prior to deferiprone treatment, and
2) on treatment (following initiation of deferiprone)
3) following discontinuation of deferiprone.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
09/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

1. Provide the following information for Studies LA20-BA and LA21-BE.
    - Drug product lots used for the studies
    - For each product lot provide
        - API supplier
        - Product formulation
        - Product batch size
        - Test results
        - Any other available information

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
09/02/2011

Miller, Mara Bauman

From: Miller, Mara Bauman
Sent: Thursday, September 01, 2011 2:59 PM
To: 'Evan Richardson'
Cc: Lynda Sutton
Subject: NDA 021825

Hello Evan,

Please confirm whether or not ApoPharma intends to market Ferriprox as a bottle without a carton. We have the bottle labels but do not see carton labels.

Thank you,
Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

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

/s/

MARA B MILLER
09/02/2011

Miller, Mara Bauman

From: Ali Ibrahim, Ebla
Sent: Monday, August 29, 2011 12:44 PM
To: 'Evan Richardson'
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hello,

Please explain, for Appendix 1 and 2 tables in the attached responses, why the N for total patients treated with any dose of deferiprone is 222 or 227 instead of 264.
Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Friday, August 26, 2011 2:42 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

Please find attached below a ZIP file containing the final response to both IRLs dated 24 August 2011.

Please note that the response to item #2 of the most recent IRL received has been updated as we have provided two possible ways of tabulating the data; there are no changes to the table that was sent yesterday, just an additional table and an updated footnote. The official submission via the ESG will follow later today.

Evan

(See attached file: Responses to 110824 IRLs.zip)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220

Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>	To	'"Evan Richardson"' <erichard@cato.com>
	cc	"Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>
08/26/2011 08:18 AM	Subject	RE: NDA 021825 Information Request

Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 10:18 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

ApoPharma is providing safety data collected during the 12 + 3 month period that the patients were nominally included in LA36-0310 in Tables 1 to 15 of the attached file. Safety information for the 222/264 patients included in LA36-0310 for which safety data were available up to the one year on therapy plus 3 months, consistent with the interval in which the patients were exposed for the LA36-0310 analysis. Please note safety data were not available for study LA-12 or the Borgna-Pignatti natural history study (n=37) or for 5 patients from study LA-03 in Toronto where safety data during the first 1 year + 3 months of deferiprone use (interval of analysis for LA36-0310) were not available.

Also provided to you earlier today were safety data collected during the entire duration of the study in which the patient was originally enrolled. Tables 1 to 15 of the earlier e-mail included safety information for the 227/264 patients included in LA36-0310 for which safety data were available up to the data cut-off date of 31 August 2010. Please note safety data were not available for study LA-12 or the Borgna-Pignatti natural history study.

As I mentioned earlier, ApoPharma will be officially submitting all of the information that has been provide today via email in an NDA amendment on 26 August.

Evan

_____
Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>	To	"'Evan Richardson'" <erichard@cato.com>
08/25/2011 04:58 PM	cc	"Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>
	Subject	RE: NDA 021825 Information Request

Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 4:52 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

Please find attached below the populated table in response to item #2 of the latest information request.

FYI, ApoPharma plans to officially submit the responses to both 24 August 2011 Information Requests in an NDA amendment tomorrow.

Regards,

Evan

(See attached file: 11-0825l Resp due 25 Aug_populated table.pdf)

_____
Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>	To	"'Evan Richardson'" <erichard@cato.com>
08/25/2011 04:12 PM	cc	"Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>
	Subject	RE: NDA 021825 Information Request

Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 12:37 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

In order to provide you with the requested information as quickly as possible, I will be emailing responses to the 2 parts of the request separately.

Please find attached below a ZIP file containing the 15 tables requested in part 1 of yesterday's information request. I will follow-up later this afternoon with our response to part 2.

Regards,
Evan

(See attached file: LA36 2b updated for 227 SF patients.zip)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

08/25/2011 11:08 AM

To: "'Evan Richardson'" <erichard@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

cc: "Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>

Subject: RE: NDA 021825 Information Request

Thank you for the information.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 10:57 AM
To: Miller, Mara Bauman
Cc: Allen Cato; Ali Ibrahim, Ebla; Lynda Sutton
Subject: Re: NDA 021825 Information Request

Hi Ebla,

ApoPharma is working hard to respond to this latest request; however, it is unlikely that they will have a response ready by 12:00 PM. We'll provide the response as soon as possible, and I will update you as more information becomes available.

Regards,

Evan

_____
Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

"Miller, Mara Bauman"
<Mara.Miller@fda.hhs.gov>

08/24/2011 04:41 PM

To: '"Evan Richardson"' <erichard@cato.com>

cc: "Lynda Sutton" <lsutton@cato.com>, "Allen Cato" <acato@cato.com>, "Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

Subject: NDA 021825 Information Request

Hello Evan,

Attached is a new information request for NDA 021825 (including a word document with the table referenced in the request). If possible, please provide a response via email by 12:00 PM, Thursday August 25. If this is not possible, please inform Ebla Ali Ibrahim of the time it will be ready.

Thank you,
Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

[attachment "InformationRequest_NDA021825_24AUG11.pdf" deleted by Evan Richardson/CRD/Cato]
[attachment "N21825 Efficacy Parameter evaluable for 082411.doc" deleted by Evan Richardson/CRD/Cato]

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

/s/

MARA B MILLER
09/02/2011

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Monday, August 29, 2011 12:45 PM
To: Robie Suh, Kathy M; Shashaty, George
Subject: RE: NDA 021825 Information Request

Done. Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Robie Suh, Kathy M
Sent: Monday, August 29, 2011 12:28 PM
To: Ali Ibrahim, Ebla; Shashaty, George
Subject: RE: NDA 021825 Information Request

Hi ebla,

Can you please ask the sponsor to explain for the Appendix 1 and 2 tables in their attached responses, why the N for total patients treated with any dose of deferiprone is 222 or 227 instead of 264.

Thanks.

Kathy

From: Ali Ibrahim, Ebla
Sent: Friday, August 26, 2011 2:58 PM
To: Robie Suh, Kathy M; Shashaty, George
Subject: FW: NDA 021825 Information Request
Importance: High

Hello,

Please find attachment and see email below from the sponsor. Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Friday, August 26, 2011 2:42 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

Please find attached below a ZIP file containing the final response to both IRLs dated 24 August 2011.

Please note that the response to item #2 of the most recent IRL received has been updated as we have provided two possible ways of tabulating the data; there are no changes to the table that was sent yesterday, just an additional table and an updated footnote. The official submission via the ESG will follow later today.

Evan

(See attached file: Responses to 110824 IRLs.zip)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>	To	"'Evan Richardson'" <erichard@cato.com>
	cc	"Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>
08/26/2011 08:18 AM	Subject	RE: NDA 021825 Information Request

Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 10:18 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

ApoPharma is providing safety data collected during the 12 + 3 month period that the patients were nominally included in LA36-0310 in Tables 1 to 15 of the attached file. Safety information for the 222/264 patients included in LA36-0310 for which safety data were available up to the one year on therapy plus 3 months, consistent with the interval in which the patients were exposed for the LA36-0310 analysis. Please note safety data were not available for study LA-12 or the Borgna-Pignatti natural history study (n=37) or for 5 patients from study LA-03 in Toronto where safety data during the first 1 year + 3 months of deferiprone use (interval of analysis for LA36-0310) were not available.

Also provided to you earlier today were safety data collected during the entire duration of the study in which the patient was originally enrolled. Tables 1 to 15 of the earlier e-mail included safety information for the 227/264 patients included in LA36-0310 for which safety data were available up to the data cut-off date of 31 August 2010. Please note safety data were not available for study LA-12 or the Borgna-Pignatti natural history study.

As I mentioned earlier, ApoPharma will be officially submitting all of the information that has been provide today via email in an NDA amendment on 26 August.

Evan

_____
Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

To

"'Evan Richardson'" <erichard@cato.com>

08/25/2011 04:58 PM

cc "Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

Subject RE: NDA 021825 Information Request

Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 4:52 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

Please find attached below the populated table in response to item #2 of the latest information request.

FYI, ApoPharma plans to officially submit the responses to both 24 August 2011 Information Requests in an NDA amendment tomorrow.

Regards,
Evan

(See attached file: 11-0825l Resp due 25 Aug_populated table.pdf)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>
"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>
08/25/2011 04:12 PM

To "'Evan Richardson'" <erichard@cato.com>

cc

"Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

Subject

RE: NDA 021825 Information Request

Thank you.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 12:37 PM
To: Ali Ibrahim, Ebla
Cc: Allen Cato; Lynda Sutton; Miller, Mara Bauman
Subject: RE: NDA 021825 Information Request

Hi Ebla,

In order to provide you with the requested information as quickly as possible, I will be emailing responses to the 2 parts of the request separately.

Please find attached below a ZIP file containing the 15 tables requested in part 1 of yesterday's information request. I will follow-up later this afternoon with our response to part 2.

Regards,
Evan

(See attached file: LA36 2b updated for 227 SF patients.zip)

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

"Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

08/25/2011 11:08 AM

To

"'Evan Richardson'" <erichard@cato.com>, "Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

cc

"Allen Cato" <acato@cato.com>, "Lynda Sutton" <lsutton@cato.com>

Subject

RE: NDA 021825 Information Request

Thank you for the information.

Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, August 25, 2011 10:57 AM
To: Miller, Mara Bauman
Cc: Allen Cato; Ali Ibrahim, Ebla; Lynda Sutton
Subject: Re: NDA 021825 Information Request

Hi Ebla,

ApoPharma is working hard to respond to this latest request; however, it is unlikely that they will have a response ready by 12:00 PM. We'll provide the response as soon as possible, and I will update you as more information becomes available.

Regards,
Evan

Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

"Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>
"Miller, Mara Bauman" <Mara.Miller@fda.hhs.gov>

08/24/2011 04:41 PM

To

"'Evan Richardson'" <erichard@cato.com>

cc

"Lynda Sutton" <lsutton@cato.com>, "Allen Cato" <acato@cato.com>, "Ali Ibrahim,

Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>

Subject

NDA 021825 Information Request

Hello Evan,

Attached is a new information request for NDA 021825 (including a word document with the table referenced in the request). If possible, please provide a response via email by 12:00 PM, Thursday August 25. If this is not possible, please inform Ebla Ali Ibrahim of the time it will be ready.

Thank you,
Mara

Mara Miller, MA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Hematology Products
WO22, Room 2309
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0683 (phone)

[attachment "InformationRequest_NDA021825_24AUG11.pdf" deleted by Evan Richardson/CRD/Cato]
[attachment "N21825 Efficacy Parameter evaluable for 082411.doc" deleted by Evan Richardson/CRD/Cato]

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

/s/

EBLA ALI IBRAHIM
08/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

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

1. Regarding your response to the information request sent August 15, 2011 (received August 23, 2011) please generate Tables 1 through 15, including only the 264 patients included in the primary efficacy analysis of serum ferritin.

2. Please populate the following table (where N is number of patients).

Efficacy Parameter evaluable for:	N
Serum ferritin (N=264)	
and LIC	xxx
and cardiac MRI T2*	xxx
and LIC and cardiac MRI T2*	xxx
serum ferritin only	xxx
LIC (N=114)	
and serum ferritin	xxx
and cardiac MRI T2*	xxx
and serum ferritin and cardiac MRI T2*	xxx
LIC only	xxx
Cardiac MRI T2* (N=39)	
and LIC	xxx
and serum ferritin	xxx
and LIC and serum ferritin	xxx
Cardiac MRI T2* alone	xxx

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
08/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825

INFORMATION REQUEST

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your August 19, 2011 submission, containing a response to the information request dated August 17, 2011.

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

1. There are some discrepancies between the Agency's results and ApoPharma's results regarding the number of subjects for the different studies for serum ferritin based on dataset la36cohort (see table below). Please clarify.

Number of subjects and number of eligible subjects by study for serum ferritin

Study ID	Total N		N for eligible patients	
	FDA	ApoPharma	**FDA**	ApoPharma
LA_01	**32**	35	**8**	8
LA_0206	**151**	151	**59**	65
LA_03	**22**	24	**7**	8
LA_04	**165**	157	**58**	56
LA_08	**28**	25	**7**	7
LA_11	**23**	23	**12**	12
LA_12	**61**	69	**22**	19
LA_15	**29**	29	**18**	18
LA_16	**29**	29	**5**	5
LA_28	**8 3**	8	**24**	3
LA_30	**25**	100	**15**	36
BP	**86**	96	**26**	27
LA_10	**10**		**3**	
Total	**744**	746	**264**	264

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
08/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

1. Provide the list of the cohorts that the Independent Selection Committee provided to ApoPharma.

2. Clarify how ApoPharma defined "Ethnic Origin" for study LA36-0310 and what "Ethnic Origin" represents.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
08/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

1. Provide the following information for the 264 patients enrolled in Study LA36-0310:
   (a) the number of patients treated at each of the various doses of deferiprone
   (b) the distribution of underlying diseases among the patients (e.g., how many had beta-thal, hemoglobin E, etc.)

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
08/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

1. For some of the studies contributing patients to Study LA36-0310 there appear to be discrepancies between the patients indicated as having been treated with deferiprone and completed study in the 1/29/09 submission and the numbers of patients indicated as eligible for inclusion in Table 6.1-1 in the study report for LA36-0310 (e.g., in the 1/29/09 submission for LA-03 there appear to be 29 patients treated with deferiprone of which 25 completed; but in Table 6.1-1 of the current submission the total N is given as 24). For each study which contributed patients to Study LA36-0310 please provide numbers of patients enrolled and treated with deferiprone in the original study as reported in your 1/29/09 submission. Where those numbers are not the same as Total N in Table 6.1-1 in the study report for LA36-0310, please explain.

2. To help us in evaluating the safety of deferiprone in the subpopulation of patients being targeted for approval please provide:
    a. A figure analogous to Figure 5.1.1 in the Safety Update Report (dated 3/31/11) including only those patients enrolled in Study LA36-0310
    b. Tables analogous to the following tables in the Safety Update Report (dated 3/31/11) including only those patients enrolled in Study LA36-0310: Tables 2.1-1; 3.1-1; 3.2-1; 4.1-1; 4.1-2; 4.1-3; 4.1-4; 4.3-1; 4.3-2; 4.4-1; 5.1-1; 5.1-2; 6.1-1; 7.1-1; 7.1-2; 7.1-3

3. Provide a graph like Figure 7.4.1-2 showing the change in ferritin over only the first 12 months of treatment.

4. Regarding the process for selecting patients for inclusion into LA36-0310, please provide the following information:
    a. Of the 746 patients potentially able to be enrolled on the trial, how many patients were not forwarded by the Independent Party to ApoPharma for possible enrollment on the trial?
    b. Did the Independent Party have knowledge of what chelator was used in the patients prior to receiving deferiprone (including dosage actually received, length of use, compliance with dosing, etc)?

5. Provide a table that lists the patients who were not enrolled in LA36-0310 by ApoPharma who were accepted for possible enrollment by the Independent Party and the reasons for their non-enrollment by ApoPharma.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
08/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

CATO Research Ltd.
U.S. Agent for ApoPharma Inc.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We refer to your February 22, 2011 submission. We also refer to your June 22, 2011 submission, containing the response to our Chemistry, Manufacturing, and Controls Information Request letter dated June 16, 2011.

We are reviewing the Chemistry, Manufacturing, and Controls and Biopharmaceutics sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Biopharmaceutics

Under Module 3.2.P.2.2.3 (p. 51), you indicated that 0.1 N HCl was chosen as the proposed dissolution medium and paddle speed of 50 rpm was also chosen. You also provided (p. 31) the Formulation development: Comparative dissolution profiles (3.2.P.2.2.1, Attachment 3). However, those batches employed were not the to-be-marketed (TBM) formulation (No. F7) nor were manufactured at the proposed manufacturing site.

In the meantime, you also included in 3.2.P.2.2.3 (p. 53) Physiological and Biological properties: Dissolution profiles of deferiprone 500 mg tablets throughout the physiological pH range (Attachment 1), the dissolution data of two batches (80434A and 90969F) (b) (4) . Those two stability batches were made using the TBM formulation (No. F7).

Please clarify which dissolution medium, 0.1N HCl or (b) (4), would be your proposed dissolution medium.

- If 0.1N HCl is chosen as the dissolution medium, please provide individual and mean dissolution data and mean dissolution profiles of the biobatch or stability batches manufactured using the TBM formulation (No. F7), similar to batches, 80434A and 90969F.

- If the (b) (4) is chosen, please provide the composition (b) (4) .

Chemistry, Manufacturing and Controls

1) Your response to comment 1 indicates that validation studies for the analytical methods to be used for bulk drug substance testing at the Apotex Pharmachem site will not be submitted prior to NDA approval, therefore this site should be withdrawn from the application. A commitment to submit validation studies in the future is not sufficient to support approval of the application with this site as a potential supplier of bulk drug substance.

2) Regarding the response to comment 13:
   a) Revise the proposed post-approval stability protocol for drug product to include the sampling of tablet lots manufactured with bulk drug substance from each proposed source and the extension of the expiry period only after sufficient data from acceptable room temperature studies on drug product made with drug substance from each source have been submitted.

   b) The stability studies on tablets manufactured with drug substance from (b) (4) were performed by Apotex Research Pvt. Ltd. (India). Specify whether this site will be used to perform stability studies after approval of the NDA.

3) Revise the criterion for Unidentified Degradation Products in the drug product specification to report all compounds observed at or above the proposed limit, not just the largest observed unknown.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

SARAH P MIKSINSKI
08/10/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021825

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

ApoPharma Inc.
c/o: CATO Research Ltd.
4364 South Alston Avenue
Durham, North Carolina 27713-2220

ATTENTION: Lynda Sutton
Chief Regulatory Officer

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deferiprone Tablets, 500 mg.

We also refer to your April 29, 2011, correspondence, received April 29, 2011, and your July 27, 2011, amendment, received July 27, 2011, requesting review of your proposed proprietary name, Ferriprox. We have completed our review of the proposed proprietary name, Ferriprox and have concluded that it is acceptable.

The proposed proprietary name, Ferriprox, will be re-reviewed 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 29, 2011 and proposed distribution as stated in your July 27, 20011, submissions 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 Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Mara Miller at (301) 796-0683.

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

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

/s/

CAROL A HOLQUIST
07/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a written response by July 25, 2011 in order to continue our evaluation of your NDA.

1) Study LA08-9701 was a study comparing the use of deferiprone plus deferoxamine versus deferoxamine alone in thalassemia patients with transfusional hemosiderosis. Of the total of 25 subjects, 7 were determined to be eligible for inclusion in Study LA36-0310. Explain why patients entered into LA08-9701 should be included in Study LA36-0310, since the efficacy of deferiprone alone does not appear to be determinable from the data generated in LA08-9701, since those patients were also receiving deferoxamine. (We note the unplanned subgroup analysis [Success rate 118/236] for Ferriprox monotherapy in Table 7.4.1-5).

2) Study LA-11 was a study of the use of deferiprone in patients in Thailand with Hgb E-thalassemia who were not transfusion dependent or required only infrequent transfusions. In that study, 16 patients had an LIC determined by biopsy before and after therapy with deferiprone. Explain why these patients were not included in Table 6.1-2 (Number of eligible patients by study for liver iron concentration). In addition, the decline in serum ferritin in this study is much greater than in the other studies with deferiprone. Other than the fact that these persons had no or few transfusions, provide any explanations of why the result in this study appears to be an outlier.

3) Study LA15-002 was a study of the use of deferiprone in patients in Iran with thalassemia. The decline in serum ferritin after only 3 months of therapy is far greater

than in any of the other trials with deferiprone, and also appears to be much greater and faster than with other iron chelators. Provide any explanations of why the result in this study appears to be an outlier.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
07/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

We are reviewing your submission and have the following information requests. We request a response by Monday July 11, 2011, in order to continue our evaluation of your NDA.

1) Provide financial disclosures for the non-ApoPharma members of the Independent Selection Committee (b) (6).

2) For study LA04 (Compassionate Use Treatment Protocol), for the 35 patients who did not have thalassemia (myelodysplastic syndrome, 15 patients; sickle cell disease, 5 patients; myelofibrosis, 4 patients; congenital anemias, 2 patients; and PRCA, aplastic anemia, Blackfan-Diamond, CLL, hereditary hemolytic anemia, refractory anemia, hemolytic anemia, Aase syndrome and transfusion dependent hemolytic anemia, 1 patient each) provide:
    a. The evidence for refractoriness to other chelating agents, case report forms and all follow-up, including all outcomes, for all patients who did not have thalassemia as the cause of anemia for which transfusions were given.
    b. An analysis of serum ferritin, LIC and MRI T2* and of all safety assessments in all patients who did not have thalassemia as the cause of anemia for which transfusions were given.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
06/27/2011

Lambert, Tu-Van

From: Lambert, Tu-Van
Sent: Thursday, June 16, 2011 10:58 AM
To: 'Evan Richardson'
Cc: Lynda Sutton; Miller, Mara Bauman
Subject: RE: Follow-up to phone call, re: NDA21-825

Dear Mr. Richardson,

We are reviewing the Chemistry, Manufacturing and Control section of your NDA and have the following comments.

1. Under Module 3.2.P.2.2.3 Attachment 2, (p. 69) you provided the dissolution development report for deferiprone tablets (Exferrum). Please clarify:

   - If the Exferrum tablet has exactly the same composition/formulation as the to-be-marketed Ferriprox 500 mg tablets (formulation no. F7).

   - If the Exferrum tablet formulation/composition is not the same as that for the Ferriprox tablet, please provide a justification for the dissolution methodology and specifications for Ferriprox as the data was generated using a different formulation.

2. You reportedly made several changes to the assay methods during the drug development. Therefore, for the two batches of drug products, i.e., batch nos. 80434A (a clinically tested and also the primary stability batch) and batch no. 90696F (a primary stability batch), that were submitted under Module 3.2.P.2.2.3 Attachment 1 (p.53), please verify the assay method employed and provide its assay method validation report.

   The composition/formulation of the batch no. 90696F could not be located in the NDA, please indicate that whether the composition/formulation of batch no. 90696F is the formulation no. F7.

Please confirm that you have received this. It would be most appreciated if you can give us an idea of when you can provide your formal response.

Feel free to contact me if anything is needed.

Kindly,
Tu-Van

Tu-Van Le Lambert
Product Quality Regulatory Project Manager
ONDQA/OPS/CDER
U.S. Food and Drug Administration

10903 New Hampshire Avenue
Building 21, Room 2625
Silver Spring, MD 20993
Phone: (301) 796-4246
Fax: (301) 796-9748

From: Evan Richardson [mailto:erichard@cato.com]
Sent: Thursday, June 16, 2011 10:11 AM
To: Lambert, Tu-Van
Cc: Lynda Sutton; Miller, Mara Bauman
Subject: Follow-up to phone call, re: NDA21-825

Ms. Lambert,

Lynda Sutton is not in the office this morning, and so Leo DiNapoli passed along your telephone message to me, as I am also a member of the project team working with ApoPharma on NDA 21-825.

Please send your information request to Ms. Sutton (copied on this email) and me, and we'll ensure that your request is quickly passed along to and addressed by ApoPharma.

Regards,
Evan

_____
Evan M. Richardson, B.S., R.A.C.
Associate Director, Regulatory Operations
Cato Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220
Tel: 919.361.2286
Fax: 919.361.2290
erichard@cato.com

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

/s/

TU-VAN L LAMBERT
06/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your February 25, 2011 submission containing a response to an FDA general advice letter dated December 2, 2009 and your June 7, 2011 submission containing a response to an FDA information request dated June 3, 2011.

We are reviewing the Container Label section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. [redacted] (b) (4) Otherwise, delete it.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
06/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) Tablets.

We also refer to your February 25, 2011 submission, containing a response to FDA general advice letter dated December 2, 2009.

We are reviewing the Container Label section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We acknowledge that your revised container label implements our previous recommendations; however, the presentation of strength is not adequately prominent. Increase the font size for the strength presentation and center it directly beneath the established name presentation. The strength presentation should be more prominent than the net quantity presentation. Submit a revised label to the application.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
06/03/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health: Maternal Health Team	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Mara Miller, Division of Hematology Products, 301-796-0683

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 12, 2011		NDA 021825	Class 2 Resubmission	April 14, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ferriprox (Deferiprone)		Iron Chelator	September 13, 2011

NAME OF FIRM: ApoPharma, 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: NDA 021825 (SDN 59) is a Class 2 Resubmission for Ferriprox (deferiprone) tablets to address deficiences in the November 30, 2009 complete response letter. Please review sections of the proposed label as they relate to pregnancy and lactation.

This is an electronic submission. Resubmission on April 14, 2011:
EDR Location: \\CDSESUB1\EVSPROD\NDA021825\0056
Label submitted April 29, 2011: EDR Location: \\CDSESUB1\EVSPROD\NDA021825\0057

Medical Officer: George Shashaty
RPM: Mara Miller, 301-796-0683

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
	☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND

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

/s/

MARA B MILLER
05/12/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Pediatric and Maternal Health: Pediatric Team	Mara Miller, Division of Hematology Products, 301-796-0683

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 12, 2011		NDA 021825	Class 2 Resubmission	April 14, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ferriprox (Deferiprone)		Iron Chelator	September 13, 2011

NAME OF FIRM: ApoPharma, 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: NDA 021825 (SDN 59) is a Class 2 Resubmission for Ferriprox (deferiprone) tablets to address deficiences in the November 30, 2009 complete response letter. Please review subsection 8.4 Pediatric Use under the "Use in Specific Populations" section.

This is an electronic submission. Resubmission on April 14, 2011:
EDR Location: \\CDSESUB1\EVSPROD\NDA021825\0056
Label submitted April 29, 2011: EDR Location: \\CDSESUB1\EVSPROD\NDA021825\0057

Medical Officer: George ShashatyRPM:
Mara Miller, 301-796-0683

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
	☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND

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

/s/

MARA B MILLER
05/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (Deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

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

- The Agency has checked the SAS data sets and SAS programs submitted as part of your electronic resubmission. They are not accessible. Please check the data sets and programs and resubmit.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
05/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825 **INFORMATION REQUEST**

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox (Deferiprone) Tablets.

We also refer to your April 14, 2011 submission containing a response to the Agency's November 30, 2009 Complete Response Letter.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA. Submit this information by Friday May 6, 2011:

1. Complete the attached table of clinical pharmacology highlights.

If you have any questions, call me at 301-796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.

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

/s/

MARA B MILLER
05/02/2011

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	Mara Miller, RPM; OODP/DHP, 301-796-0683

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
April 27, 2011		NDA 021825	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Deferiprone	N/A	Metal Chelator	September 9, 2011

NAME OF FIRM:	
ApoPharma, Inc	PDUFA Date: October 14, 2011

TYPE OF LABEL TO REVIEW

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

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA/BLA (Class 2 Resubmission)
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA021825\0056
* Label was not included and has been requested; Carton/Container Labeling submitted in an earlier submission on February 25, 2011

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:

Mid-Cycle Meeting: July 6, 2011

Labeling Meetings: To Be Scheduled

Wrap-Up Meeting: To Be Scheduled (week of September 12, 2011)

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

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

/s/

MARA B MILLER
04/27/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021825

ACKNOWLEDGE – CLASS 2 RESPONSE

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

We acknowledge receipt on April 14, 2011 of your April 13, 2011 resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) 500 mg Film-Coated Tablets.

We consider this a complete, class 2 response to our November 30, 2009 action letter. Therefore, the review goal date is October 14, 2011.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, M.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

MARA B MILLER
04/26/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Interdisciplinary Review Team for QT Studies	Mara Miller, OODP/DHP, 301-796-0683

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 20, 2011		021825	NDA Class 2 Resubmission	April 13, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ferriprox (deferiprone)	Standard		June 15, 2011

NAME OF FIRM: ApoPharma, 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: On April 14, 2011, ApoPharma Inc. submitted a full response to the Complete Response Letter (CRL) issued by the FDA on 30 November 2009. Clinical item #4 in the CRL stated "Submit data that more thoroughly assess the arrhythmogenic potential of deferiprone. In addition to any other information, supply data from an assessment of the effect of deferiprone and its primary 3-O-glucuronide metabolite on the electrocardiographic QT interval in patients and/or healthy volunteers."

Clinical Pharmacology is requesting IRT review of ApoPharma's response to ensure adequacy of the response.

This is an electronic submission (sequence number 56):

EDR Location: \\CDSESUB1\EVSPROD\NDA021825\0056

Joe Grillo is the Clinical Pharmacology Reviewer (6-0591).

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

MARA B MILLER
04/27/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis/ Sue Kang

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Mara Miller, Office of Oncology Drug Products/Division of Hematology Products, 301-796-0683

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 25, 2010		21825	Response to General Advice	February 28, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ferriprox (deferiprone)	Standard	Metal Chelators	March 30, 2011

NAME OF FIRM: ApoPharma, 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: On October 23, 2009, Jibril Abdus-Samad, PharmD, Safety Evaluator, provided and assessment of the container label and insert labeling for Ferriprox Tablets from a medication error perspective. Review comments on the container label were sent to the applicant. On February 25, 2011 a response addressing the comments was received from ApoPharma.

This is an electronic submission.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Mara Miller	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

MARA B MILLER
02/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-825

GENERAL ADVICE

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) 500 mg Tablet.

We also refer to your November 30, 2010 submission, containing a response to our letter dated November 9, 2010 concerning Protocol LA36-0310 entitled, "A Study to Evaluate the Efficacy of Deferiprone in Patients with Iron Overload for Whom Standard Chelation Therapy Has Been Inadequate – Based on an Analysis of Data from Clinical Studies of Deferiprone."

As has been communicated to you previously, we recommend that your NDA resubmission provide evidence from existing studies or new trials in a homogeneous population of patients who have progressive iron accumulation despite adequate deferoxamine therapy or are intolerant to deferoxamine (see minutes of April 5, 2010 meeting). The study you have proposed (Protocol LA36-0310) seeks to obtain this data through use of the existing clinical trial database. Comments providing recommendations and delineating some limitations of this approach have been provided to you previously (letters dated August 3 and November 9, 2010).

We continue to have concerns about the adequacy of this approach. Nevertheless, we agree that your proposed further examination of the existing database may be of some utility in assessing the overall efficacy and safety of deferiprone. We reiterate our previous comments to you and have the following recommendations and additional comments that should be addressed in your clinical study report in your NDA resubmission.

1. Based on ICH E9, the intention-to-treat population should include all randomized subjects.

2. The overall success rate and its 95% CI should be calculated based on Pearson-Clopper exact confidence interval.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2192.

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
01/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Via Email and UPS Express Mail

NDA 021825 **GENERAL ADVICE**

Cato Research.
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA) Pilot 1 program, for Ferriprox® (deferiprone) 500 mg Tablet.

On April 24, 2010, a Food and Drug Administration (FDA) employee provided Dr. Nancy F. Olivieri with a redacted copy of the Establishment Inspection report (EIR) for a July 6-10, 2009, FDA inspection of a clinical trial of deferiprone that she had conducted. This was done pursuant to Field Management Directive (FMD)-145.[1] Certain information in the EIR pertaining to data submitted in your unapproved NDA was inadvertently not redacted from the EIR prior to its being provided to Dr. Olivieri. This information included some laboratory values reported in your NDA and whether some subjects or data were included or excluded from your analysis. We became aware of this improper redaction when we received your November 4, 2010, e-mail to Hyon-Zu Lee. According to the documents attached to your e-mail, you were contacted by the law firm Fasken Martineau DuMoulin LLP (Fasken Martineau) on November 2, 2010, regarding the EIR.

In response to this improper redaction, we are contacting Dr. Olivieri and Fasken Martineau to notify them of the improper redaction. We are requesting that both Dr. Olivieri and Fasken Martineau 1) destroy all copies (both hard and electronic) of the improperly redacted EIR in their possession, 2) not use, distribute, or disclose the improperly redacted EIR, and 3) notify any individuals or organizations with whom they may have shared that EIR, that all hard and electronic copies of it they may have should be destroyed, and those other individuals or organizations should not use, rely on, or disclose the information contained in that copy of the EIR. We also are asking Fasken Martineau to notify those individuals or organizations from whom it may have received the EIR to destroy all hard and electronic copies of it they may have, and that they should not use, rely on, or disclose the information contained in that copy of the EIR. Additionally, we are asking Dr. Olivieri and Fasken Martineau to confirm in writing, by November 26, 2010, their agreement to these requests. We are also providing Dr. Olivieri with a

[1] See http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm103299.htm

properly redacted copy of the EIR. Please note that because Dr. Olivieri is receiving the EIR from her own inspection, certain information that might not be available to another member of the public, such as the name of the protocol and information on individual subjects she enrolled, will not be redacted.

We are taking this action because the information that we have identified in the EIR as coming from your unapproved NDA is not available for public disclosure under FDA's regulations, and we do not believe that this information has been publicly disclosed by you.

We apologize for the improper redaction of your information, and assure you that we are taking steps to help ensure that this does not occur again. CDER takes its disclosure responsibilities very seriously and we make every effort to ensure that information is disclosed only in accordance with applicable laws and regulations.

If you have any questions, please call me at 301-796-3603.

Sincerely,

{See appended electronic signature page}

Nancy B. Sager
Director, Division of Information Disclosure Policy
Center for Drug Evaluation and Research

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

/s/

NANCY B SAGER
11/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-825 **INFORMATION REQUEST**

Cato Research Ltd.
Attention: Lynda Sutton, B.S.
U.S. Agent for ApoPharma, Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) 500 mg Tablet.

We also refer to your June 21, 2010 submission, containing your clinical protocol entitled "A Study to Evaluate the Efficacy of Deferiprone in Patients with Iron Overload for Whom Standard Chelation Therapy Has Been Inadequate – Based on an Analysis of Data from Clinical Studies of Deferiprone."

We have reviewed the referenced material and have the following comments and requests for information. We have a number of concerns raised by your proposed study as the basis for determining the efficacy and safety of the use of deferiprone for the proposed indication:

Patient population

1. The title of the protocol suggests that the indication may apply to all patients with transfusional iron overload. Virtually all the patients studies in your studies had thalassemia as the cause of anemia for which transfusions were required. Unless there are data supplied for patients with other causes of chronic anemia and the need for transfusion therapy (sickle cell disease, myelodysplastic syndrome, aplastic and other anemia), the indication should be restricted to patients with thalassemia.

Endpoints

2. In regard to serum ferritin, while it is believed that levels in excess of 2500 mcg/L are associated with a worse outcome in patients with thalassemia compared to in patients with a level less than 2500 mcg/L, there are no data that a 20% decrease in serum ferritin confers any clinical benefit for a patient (for example, decreasing the serum ferritin from 5000 mcg/L to 4000 mcg/L). Yet this change would be considered a success for a patient treated with deferiprone.

3. In regard to liver iron concentration (LIC), your use of the results of deferasirox Study 0107 [The proposed 20% reduction in SF or MRI T2* is based on the 17% reduction in LIC from baseline (from 14.1 to 11.7 mg Fe/g dw) observed during therapy with deferasirox in the pivotal study 0107] as a comparator does not take into account the fact that persons in Study 0107 were initially dosed based on baseline LIC, some done by superconducting quantum interference device (SQUID) which is known to underestimate the LIC, and were therefore given a dose that was less than what is now known to be therapeutic. Additionally, as with other chelators, those with higher body iron burdens tend to be more responsive to chelator therapy compared to those with a lesser body iron burden. Currently, it is believed that patients with LIC < 7 mg Fe/g dw are not generally subject to the adverse effects of iron toxicity in most body organs. The clinical significance of a decrease of ≥ 20% in LIC is not known.

4. In regard to cardiac MR1 T2*, as was the problem with the data provided in the Study LA 16-0101, we are not aware of any data that show that an increase in T2* of 20% or greater in a patient with a baseline T2* of < 20 ms has any clinically meaningful significance.

5. You will claim success for any patient whose defined improvement occurs in ANY of these variables, rather than in ALL of the variables (for example, a fall in serum ferritin would be a success even if the LIC were rising and the T2* were falling in the same patient). Such inconsistencies among the findings for the efficacy parameters among and within patients would weaken the persuasiveness of the results.

Definition of failure of other chelating agents

6. The protocol does not state the length of treatment time nor the rate of fall in serum ferritin (or LIC or T2* for that matter) that the person must have experiences while receiving other chelation therapy before being considered a failure on that therapy. For instance, if the patient had been receiving other chelation therapy for nine months and the serum ferritin had fallen from 9000 mcg/L to 3000 mcg/L, that person could be considered to be a failure and would be eligible to be enrolled in the study even though there had clearly been some response to therapy.

7. The dose of deferoxamine that the patient may have been receiving (20-40 mg/kg/day) when declared to be a failure appears to be too low to make that declaration. Although the label for deferoxamine states that the dose is 20-40 mg/kg/day, in practice, the dose administered often is increased to up to 50 mg/kg/day if adverse reactions are not encountered.

Study design and validity of data

8. This is a retrospective analysis of data already accumulated. There must be rigid rules in the protocol that spell out the exact methods for eliminating bias in the study.

9. To help ensure objectivity and minimize bias, there will need to be a separate group to review the data for eligibility to enroll in the trial and another group to analyze the data for efficacy and safety. Data cannot be shared between the two groups.

10. For many of the studies referenced to be included in the study, there did not seem to be patients who were commenced on deferiprone because of failure while receiving another chelation agent. You must use the utmost care in adhering to the inclusion/exclusion criteria established for the study.

Statistical Comments

11. The draft protocol that was submitted contains only limited statistical information. Submit a protocol with a detailed statistical analysis plan which includes detailed sample size justification and detailed subgroup analysis plans. Also provide detailed strategy and justifications for reviewing data from multiple retrospective studies to reduce bias.

12. Keep missing data to a minimum. Address the missing data in the primary analysis. Provide a justification for your choice of LOCF imputation or any other intended method of imputation. Perform sensitivity analyses that evaluate the limitations of the data.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Acting Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

ANN T FARRELL
08/03/2010

MEMORANDUM OF THE MEETING

MEETING DATE: April 5, 2010
TIME: 2 PM – 3 PM (EST)
LOCATION: Conference Room 1417 (White Oak)
APPLICATION: NDA 21-825
DRUG NAME: Deferiprone Tablets
TYPE OF MEETING: End of Review Conference

MEETING CHAIR: Ann Farrell, M.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Office of Oncology Drug Products:
Richard Pazdur, M.D., Director

Division of Hematology Products:
Ann Farrell, M.D., Acting Director
Edvardas Kaminskas, M.D., Acting Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
George Shashaty, M.D., Medical Reviewer
Robert Kane, M.D., Acting Deputy Director for Safety
Albert Deisseroth, M.D., Medical Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Division of Biometrics V:
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Mark Rothmann, Ph.D., Statistics Team Leader
Satish Misra, Ph.D., Statistics Reviewer

Office of Surveillance and Epidemiology:
Sue Kang, Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

ApoPharma:
Michael Spino, B.Sc.Phm., Pharm.D., President
Fernando Tricta, M.D., Vice President, Medical Affairs
Lopa Bandyopadhyay, Manager, Regulatory Affairs
Kai Mardy, Project Leader
Yu Chung Tsang, Ph.D., Biostatistics

Cato Research:
Allen Cato, M.D., Ph.D., President
Lynda Sutton, B.S., Chief Regulatory Officer

Consultant:
(b) (4)

BACKGROUND AND PURPOSE OF THE TELECONFERENCE:

The NDA for deferiprone was submitted under the Continuous Marketing Application (CMA)-Pilot 1 program. The Sponsor submitted the last Clinical/Statistical reviewable unit for the NDA on January 29, 2009. The Agency issued a Complete Response (CR) letter on November 30, 2009 for the NDA.

On February 26, 2010, the sponsor requested a meeting to obtain feedback on the review for the NDA, including options for the therapeutic indication and accelerated approval.

SUMMARY OF THE TELECONFERENCE:

In response to the questions in the February 26, 2010 background package, the following agreements were reached after the discussion. The format provides the firm's questions posed in the meeting background package in italics followed by DHP responses sent to the Sponsor on March 31, 2010 in bolded font and the discussions during the teleconference in regular font.

Preamble

For accelerated approval, you will need to provide evidence from existing studies or new trials in a homogeneous population of patients who have progressive iron accumulation despite adequate deferoxamine therapy or are either intolerant to deferoxamine. You must provide adequate documentation for reasons patients are intolerant to deferoxamine (i.e., dose limiting and end-organ toxicities). The study population can be comprised of various underlying diseases resulting in the need for chronic transfusion therapy producing iron overload. Provide your expected number of patients who would meet these eligibility criteria. The endpoint for accelerated approval must reasonably likely predict clinical benefit; hence, the Agency would be willing to entertain a discussion of increases in cardiac MRI T2*, decreases in serum ferritin levels and decreases in hepatic iron concentrations as possible endpoints. You should be able to provide definitions of response to each of these measurements (i.e., response definitions using cardiac MRI T2* or serum ferritin or hepatic iron concentrations). These definitions should be then prospectively applied to your defined population.

Questions:

1. *Following the teleconference with the FDA, ApoPharma reviewed the available studies in the NDA in which patients were enrolled because they were not adequately treated on their current therapy at the time. The LA-16-0102 study enrolled patients whose cardiac iron levels were not controlled by the current treatment, putting them at risk of developing iron-induced heart disease. LA-02/06 and LA-17 enrolled patients whose serum ferritin was not adequately controlled by their current treatments, which served as the basis for patient enrollment. Based on this review, ApoPharma proposes that the LA-16-0102 study serve as the pivotal study and the LA-02/06 study, together with the Borgna-Pignatti natural history study, serve as the supportive studies for the new indication, and that the publication of the LA-17-9701 study be considered as additional*

information in support of the application. Does the Agency agree that the above studies, which were included in NDA 21-825, provide relevant and suitable information to assess the proposed revised indication?

FDA Response:
Please see the preamble above.

2. *Are there other studies in the NDA that the FDA believes should be considered in support of the revised indication?*

FDA Response:
Please see the preamble above.

3. *LA-16-0102 was an RCT powered (n=61) to assess differences in the MRI T2* results between deferiprone and deferoxamine-treated patients as the primary endpoint of efficacy and it met its objective, but it employs an endpoint not previously used by the FDA to approve a new drug. The study also included both serum ferritin and liver iron concentrations (MRI T2*), but the study was not powered to demonstrate a significant difference in these parameters between the products, as it was powered only for its primary endpoint. LA-02/06 was a much larger study (n=187) where serial serum ferritin was measured over time and compared to baseline results when patients were switched from deferoxamine. Both the Borgna-Pignatti study and the LA-17-9701 studies assessed serial serum ferritin concentrations over the duration of their respective studies. Does the FDA agree that the efficacy data submitted as part of NDA 21-825 will be sufficient to assess whether or not there is substantial evidence of efficacy for use of Ferriprox in the treatment of transfusional iron overload, according to the proposed new indication?*

FDA Response:
Please see the preamble above.

4. *ApoPharma's proposed indication is "For the treatment of patients with transfusional iron overload when previous chelation therapy is contraindicated or inadequate." Does the FDA agree that this indication would be suitable for Ferriprox based on the type of information submitted?*

FDA Response:
No. In general, the indication is defined by the patient population studied. For accelerated approval, we recommend a patient population which is either intolerant to deferoxamine or has progressive iron overload while receiving adequate doses of deferoxamine. Rigorous definitions of deferoxamine intolerance and of progressive iron overload should be included.

5. *ApoPharma would like to discuss FDA's expectations and concepts for a confirmatory study as part of the accelerated approval process.*

FDA Response:
Provide your proposal for confirmatory trials.

Discussions during the meeting:

The Sponsor started the meeting with the presentation of their slides (attached) and asked if the proposed inclusion and response criteria are acceptable. They stated that there are 22 years of experience with deferiprone including 10 years of postmarketing in other countries.

The Agency noted that the proposed study entry criteria listed in slide #1 (b) (4) (b) (4) are vague. The Sponsor needs to establish objective criteria (for example, if the patient was not able to take deferoxamine, there is need for information and documentation of the dose-limiting and/or end-organ toxicities developed that precluded further treatment; for noncompliance, there is need for documentation of noncompliance - how long the patient took deferoxamine and how many doses were missed and what effort had been taken to get the patient to be compliant, etc.).

The Agency recommended that the Sponsor collect efficacy and safety data from a well-defined population of patients who are intolerant to deferoxamine (with a strict definition of the reasons why the patient is unable to take deferoxamine) or have progressive iron accumulation despite adequate deferoxamine therapy and the Sponsor should provide response criteria (including clinically meaningful rate/change) in the proposed endpoints (i.e., liver iron concentration, serum ferritin, T2*). There should be a well-defined need for deferiprone treatment (e.g., the reason the patient cannot take deferoxamine cannot be simply indicated as (b) (4) (b) (4)). The Agency noted that (b) (4) . The Agency commented that the Sponsor could define a patient population from various available studies. The Agency reiterated that the indication in the label will be defined by the patient population studied.

The Sponsor commented that LA16 was enrolling patients who developed iron overload in the heart while receiving deferoxamine and could comply with the criteria. The Agency noted that in LA16 only 29 patients received deferiprone. The number of patients who received deferiprone in LA16 is too small to make a definitive assessment of efficacy and safety. The Agency commented that deferasirox had 600 patients in the randomized trial.

The Agency reiterated that if the Sponsor wishes to pursue accelerated approval in a population that does not have available therapy, ApoPharma should develop a single arm trial with prospectively defined criteria and the trial should provide an adequate response rate.

The Agency noted that the major issue with a single arm trial for this use is the definition of the patient population. The Sponsor should define patients that had poor response to deferoxamine (for example, a poor response to deferoxamine despite an adequate trial of X duration and serum ferritin level remaining above X). Currently, the Agency regards only deferoxamine as available treatment, not deferasirox. In addition, the Sponsor should define specific criteria to be classified as a responder and the change of response that is clinically meaningful. The Sponsor should provide justification of the frequency of the response rate considered to be clinically meaningful and provide the data demonstrating durability of responsiveness (i.e., how long the response lasted).

The Sponsor commented that data on non-response to deferoxamine is hard to collect as changes in serum ferritin happen over a long period of time. The Agency again stated that the Sponsor should provide objective criteria for patients to be entered into the trial with sufficient numbers of patients to ensure confidence. The Agency commented that, alternatively, the Sponsor could perform a new trial. The Sponsor asked why the literature data cannot be used. The Agency responded that for example in the Borgna-Pignatti study, there were multiple problems including: endpoints were not interpretable, no source data were available, and patients were not randomized to treatment.

The Agency reiterated that the sponsor should provide analyzable data for review (literature can be submitted as supportive data) to respond to the complete response letter or alternatively, the Sponsor can provide a new study.

In addition, the Agency noted that although centers are using T2*, there are no data available that an increase in T2* predicts clinical benefit.

4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page;

10 Page(s) of Copyright Material has been Withheld in Full immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	GI-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
04/13/2010

MEMORANDUM OF TELECONFERENCE

Date: January 5, 2010

Time: 12:30- 1 PM

Location: White Oak Bldg 22, Rm 2327

Application: NDA 21-825: Ferriprox® (deferiprone) Tablet

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products (HFD-160)

Rafel Rieves, M.D., Director
Ann Farrell, M.D., Acting Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Team Leader, Medical
George Shashaty, M.D., Medical Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

And

External Constituent Attendees and Titles:

ApoPharma:
Michael Spino, B.Sc.Phm., Pharm.D., President
Fernando Tricta, M.D., Vice President, Medical Affairs
John Connelly, Ph.D., Vice President, Regulatory Affairs and Nonclinical Research
Lopa Bandyopadhyay, Manager, Regularory Affairs

Consultant:
(b) (4)
William Schultz, Zuckerman Spaeder LLP

Cato Research:
Allen Cato, M.D., Ph.D., President
Lynda Sutton, B.S., Chief Regulatory Officer
Vicki Gunto, Ph.D., Director, Regulatory Affairs
Evan Richardson

The Division arranged the teleconference with ApoPharma to obtain sponsor's preliminary plan to the Complete Response (CR) letter issued on November 30, 2009 for the NDA and to provide advice regarding the expanded access program.

The Division asked the sponsor's planned timeline for discussing the CR letter. The sponsor responded that they are in the process of preparing a document that addresses the deficiencies in the CR letter and are planning to include them in the meeting request to be submitted around mid-February. The sponsor expressed frustration that it would take about five years and be financially costly to perform an additional study to provide the requested safety and efficacy data in the CR letter.

The Division responded that the timeline is reasonable and noted that CR letters need to be comprehensive listing all deficiencies identified, but that the sponsor can respond (in terms of planning a post-CR letter meeting) by outlining their perspectives, justifications and creatively discussing their overall development strategy. The Division mentioned the potential for consideration of development of deferiprone for use among patients "intolerant" of other chelators and/or "refractory" to the other chelators (i.e., the situation sometimes referred to as "second line" therapy due to intolerance or failure of other therapies).

The Division noted that there is an expanded access program available to provide access to investigational drugs for patients who have serious or immediately life-threatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies. The Agency published amended rules late last year that include provisions for access for individual patients, groups of patients smaller than that typical of a treatment IND or treatment protocol, and larger populations where widespread treatment use is appropriate (the Treatment IND). Also, the Division noted that the new rule provides regulations regarding the recovery costs of an investigational drug.

The sponsor commented that there are about 40 US patients that are receiving deferiprone through single patient INDs (SPIs) and noted that the SPI pathway is time consuming. In addition, most patients wait until their cardiac function is much compromised before seeking the drug through an SPI and stated that these patients are the ones that failed current treatment. The Division strongly recommended that sponsor consider the expanded access program beyond the SPI pathway.

The sponsor then noted that they submitted a letter to the NDA on December 23, 2009 requesting Dr. Olivieri's documents. The letter also included copies of e-mail communications between ApoPharma and (b) (4) regarding a study of deferiprone that was published by the latter. The Division indicated that that submission had been reviewed. The Division also responded that the Agency is consulting the legal team internally and that the inspection of the LA-01 and LA-03 study sites are not closed out at this time, but that the sponsor could request the information via the Freedom of Information Act (FOIA). The sponsor commented that they do not wish to request the documents via FOIA as it would take a considerable amount of time.

The teleconference concluded.

ACTION ITEMS:

- The sponsor will submit a type A meeting request in Mid-February of 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	GI-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
01/11/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-825

GENERAL ADVICE

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma, Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) 500 mg Tablet.

We also refer to our Complete Response letter dated November 30, 2009, containing the deficiencies for the NDA.

Listed below are our recommendations for the container label for your consideration if you decide to resubmit the NDA.

Container Label:

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

2. Delete or decrease the prominence of the butterfly graphic on the principal display panel to ensure the proprietary and established names and strength are the most prominent information on the principal display panel.

3. Relocate the strength (500 mg) from the bottom of the principal display panel to immediately follow the established name and dosage form as this is the usual location for this information and in its current location takes longer to locate on the label. For example:

Ferriprox
(Deferiprone) Tablets
500 mg

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

RAFEL D RIEVES
12/02/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 21-825 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Ferriprox Established/Proper Name: deferiprone Dosage Form: Tablet		Applicant: ApoPharma, Inc. Agent for Applicant (if applicable): Cato Research (Lynda Sutton)
RPM: Hyon-Zu Lee, Pharm.D.		Division: Division of Medical Imaging and Hematology Products

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ 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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	November 30, 2009
❖ Actions	
• Proposed action	☐ AP ☐ TA ☐ AE ☐ NA ☒ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

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

❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance 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 Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ 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] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) November 30, 2009 (CR)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Sept. 21, 2009 (not sent to the sponsor).
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	July 9, 2009
• Original applicant-proposed labeling	June 27, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Foreign Labeling (submitted by the sponsor on Jan. 29, 2009)
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None

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

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	July 9, 2009
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 September 4, 2009 Acceptable (Sept. 11, 2009)
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM October 20, 2009 ☒ DMEDP January 30, 2007, Oct. 23, 2009 ☐ DRISK ☒ DDMAC August 26, 2009 ☐ CSS ☒ Other reviews Pediatrics (Sept. 17, 2009) MHT (Sept 24, 2009)
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	PM: March 11, 2009 STATS: March 24, 2009 CMC: March 27, 2007
❖ 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 in 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
❖ Pediatric Page *(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
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	

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

• PeRC *(indicate date of mtg; approvals only)*	☒ Not applicable
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg April 24, 1997, Oct. 9, 2001, Oct. 10, 2001, July 9, 2004, May 15, 2006
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None Nov. 20, 2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Nov. 25, 2009
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review (Nov. 25, 2009)
• Clinical review(s) *(indicate date for each review)*	Oct. 19, 2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See MO review dated October 19, 2009 (pages 81-102).
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See MO review dated October 19, 2009 (page 19).
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DCRP: April 20, 2009, Medical Imaging: April 28, 2009 CDRH/OSEL/DP: July 26, 2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Oct. 14, 2009 ☐ None Oct. 22, 2009
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested August 14, 26 and Oct.14, 2009 (2) (letters) Oct. 30, 2009 (review summary)

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

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None November 22, 2009
Statistical Review(s) *(indicate date for each review)*	☐ None November 10, 2009
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 March 27, 2008, Sept. 24, 2009, Oct. 22, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None June 27, 2007, September 22, 2009.
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) *(indicate date for each review)*	☐ None March 21, 2008, April 7, 2008, October 20, 2009
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	

☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC review dated March 21, 2008.
☐ Review & FONSI *(indicate date of review)*	N/A
☐ 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)*	Date completed: Oct. 19, 2009 ☐ Acceptable ☒ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
11/30/2009

MEMORANDUM OF TELECONFERENCE

Date: October 29, 2009

Time: 9:30-10 AM

Location: White Oak Bldg 22, Rm 1311

Application: NDA 21-825: Ferriprox® (deferiprone) Tablet

Between

FDA Attendees:

CDER Office of New Drugs:
John Jenkins, M.D., Office Director, Office of the Director

CDER Office of Regulatory Policy:
Jane Axelrad, Associate Director for Policy

Office of the Chief Counsel:
Donna Katz, Associate Chief Counsel for Drugs

CDER Division of Medical Imaging and Hematology Products:
Rafel Rieves, M.D., Division Director
Ann Farrell, M.D., Acting Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader
George Shashaty, M.D., Medical Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

CDER Division of Scientific Investigations:
Tejashri Purohit-Sheth, M.D., Branch Chief, Good Clinical Practice Branch II
Anthony Orencia, M.D., Medical Officer

CDER Division of Information Disclosure Policy:
Nancy Sager, Director

And

External Constituent Attendees and Titles:

ApoPharma:
Fernando Tricta, M.D., Vice President, Medical Affairs
John Connelly, Ph.D., Vice President, Regulatory Affairs and Nonclinical Research
Lopa Bandyopadhyay, Manager, Regularory Affairs

Consultant:
(b) (4)
William Schultz, Zuckerman Spaeder LLP

Cato Research:
Allen Cato, M.D., Ph.D., President
Lynda Sutton, B.S., Chief Regulatory Officer
Vicki Gunto, Ph.D., Director, Regulatory Affairs

BACKGROUND AND MEETING PURPOSE:

FDA had a teleconference with the sponsor on September 24, 2009 to communicate that the Oncologic Drugs Advisory Committee (ODAC) meeting scheduled for October 6, 2009 has been canceled. The Agency arranged a follow up teleconference to update the review status of this NDA application.

The sponsor submitted the following questions on October 27, 2009 for the teleconference to the electronic document room. (The format provides the sponsor's questions in italics, followed by the discussions during the teleconference in regular font):

1. *How is FDA progressing on the post inspection review?*

    a. *What is the process to resolve concerns from the inspection and any third party concerns?*

    The Agency noted that the reviews are ongoing, including the review of the results of the inspection of the clinical investigator site. In addition, there are manufacturing deficiencies that are outstanding and can not be resolved during this review cycle. The Agency noted that the PDUFA due date of November 30, 2009 still stands for this NDA application.

    b. *What issues have been raised? It is important for ApoPharma to understand these so that it can respond.*

    The sponsor commented that they need to know the issues raised and stated that their assumption is that Dr. Olivieri submitted information to the Agency. They commented that they could request the information through the Freedom of Information Act (FOIA).

    c. *When can ApoPharma have access to the data from the inspections which were responsible for raising concerns, and in particular, to any data submitted by third parties?*

The Agency noted that information can be classified into two categories; the inspectional findings (which, since the inspection was conducted as part of FDA's Bioresearch Monitoring Program, are subject to the Privacy Act) and information that was submitted to the Agency outside of the inspection (which would not be subject to the Privacy Act). The Agency's ability to and process for sharing the information is potentially different depending on the route by which the information was obtained by the Agency.

The Agency also noted that there is a need to review the study (LA-01) conducted in the Canadian clinical site as the endpoints used in that study are the same as the ones used in the main confirmatory study that supported the accelerated approval of another iron chelating drug in 2005. The Agency stated that we did not have time to evaluate the inspectional findings before the advisory committee (AC) and therefore had to cancel the AC.

The sponsor commented that study LA-01 was not conducted under Good Clinical Practice, and that because they don't know exactly what information has been obtained by the Agency through the inspection and from the third party submission, they aren't able to provide the Agency with additional information that might help resolve the issues being raised.

The Agency noted that at this time, we are evaluating the extent to which the information obtained from the inspection and from outside the inspection can be shared with the sponsor, and what the appropriate mechanism for doing so might be.

2. *How can ApoPharma help FDA to resolve the open issues expediently?*

   The Agency stated that we do not have any specific requests at this time as we are working to wrap up the review of the NDA application, and are reviewing the information obtained from the inspection and from the third party.

3. *What is the plan to reschedule the Advisory Committee and take action on the pending NDA?*

   a. *What is the schedule for these events?*

      The Agency stated that new molecular entities are generally presented at an AC, but we are not planning to take this application to an AC during this review cycle. However, the Agency is working to meet the PDUFA due date.

4. *Are there any other open review items, and if so, what are they?*

   The Agency noted that there are manufacturing deficiencies in addition to other disciplinary review deficiencies such as Clinical Pharmacology issues, but as stated, we are working to wrap up the reviews.

   The sponsor asked if there are any benefits of releasing and extending the PDUFA due date.

   The Agency responded that PDUFA date extension has to be triggered by a major amendment.

   The Agency noted that this application was scheduled to be presented at the AC to discuss review issues such as demonstration of safety/efficacy and adequacy of the clinical study/database, and that the need to obtain advice from the experts still remains. The Agency noted that we are evaluating internally with the legal team what information can be shared with the sponsor regarding the third party inspection and the information submitted by the third party.

ACTION ITEMS:

- The Agency will evaluate what, and if so how, information from the inspection and the third party can be shared with the sponsor.
- The Agency will wrap up the review to meet the PDUFA due date of November 30, 2009.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	GI-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
11/03/2009

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, October 19, 2009 8:53 AM
To: Lee, Hyon-Zu
Subject: Call from Bill Shultz re deferiprone NDA

From: Jenkins, John K
Sent: Friday, October 16, 2009 5:03 PM
To: Rieves, Rafel; Pazdur, Richard; Jenkins, John K; Axelrad, Jane A; Ball, Leslie
Cc: Jenkins, John K
Subject: Call from Bill Shultz re deferiprone NDA

Dwaine and others

I had a call from Bill Shultz today. He is now the legal counsel for ApoPharma (see attached authorization from the sponsor) and he wanted to know what was going on with the NDA since the telecon we had with the company a couple of weeks ago when we told them we were going to cancel the AC meeting. He noted that the sponsor submitted a letter to the division on October 8 (attached) stating their case regarding the Canadian study site in question. He had two fundamental questions. First, he wanted to know if FDA would share with the company the information that had been submitted to FDA by the investigator. He stated his view that these documents were not protected from disclosure and that the sponsor should see them so they could respond with their side of the case. Second, he wanted to understand when FDA expected to resolve the issues and restart review of the NDA.

I explained to Bill the division's review of the NDA and the concerns that led to a request for a DSI audit of the Canadian study site even though it was presented by the sponsor as only "supporting" data. I told him that the results of that audit resulted in data submitted back to DSI that needed to be reviewed. I also told him that in parallel the investigator from the site had contacted FDA to share her concerns about the drug and that we needed to understand those allegations and data as well.

Bill was not debating our decision to cancel the AC.

I told him that I would follow up with our team to understand where things stand with the DSI review of the site audit and also to discuss the status of the information from the investigator and whether it could b shared with the sponsor. I did not give him any timeline for when this would be resolved and did not tell him what, if any, action would be taken on the NDA by the PDUFA goal date. I also asked that he focus his contacts to the Division and he agreed.

So, a few action items and questions:
1. What is the status of the DSI review?
2. Have we scheduled a meeting to include Jane and OCC to discuss this case and how to handle the information from the investigator? If not, I think we need to do this in the near future.
3. Please have the project manager for the NDA enter this e-mail in DARRTS as a record of the phone call.

John

John K. Jenkins, M.D.
Director, Office of New Drugs
10903 New Hampshire Avenue
Bldg #22, Room 6304

Silver Spring, MD 20993
301-796-0700
301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
10/19/2009

MEMORANDUM OF TELECONFERENCE

Date: September 24, 2009

Time: 10:30-11 AM

Location: White Oak Bldg 22, Rm 2376

Application: NDA 21-825: Ferriprox® (deferiprone) 500 mg Tablet

Between

FDA Attendees:

Office on New Drugs:
John Jenkins, M.D., Office Director, Office of the Director

Division of Medical Imaging and Hematology Products:
Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader
George Shashaty, M.D., Medical Reviewer
Satish Misra, Ph.D., Statistical Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Office of the Executive Programs:
Nicole Vesely, Pharm.D., Advisors and Consultants Staff

And

External Constituent Attendees and Titles:

ApoPharma:
Fernando Tricta
Michael Spino
John Connelly

Cato Research:
Lynda Sutton
Vicki Gunto

BACKGROUND AND MEETING PURPOSE:

FDA Division of Scientific Investigations (DSI) performed an inspection (from July 6 to July 10, 2009) on the Canadian clinical site (Nancy F. Olivieri M.D., Clinical Investigator, 200 Elizabeth St., Eaton Wing Room # EN10-225 Toronto) for the LA-01 study per request from the review division. LA-01 was a two year study with 71 subjects (35 in deferiprone arm, 36 in

deferoxamine arm) using liver iron concentration (LIC) and serum ferritin as efficacy endpoints (endpoints consistent with those used in the main confirmatory study that supported the accelerated approval of another iron chelating drug in 2005). The sponsor's only proposed adequate and well-controlled clinical study (LA16-0102) was a one year study with 61 subjects (29 in deferiprone arm, 32 in deferoxamine arm) proposing to use T2* as the primary endpoint.

FDA arranged the teleconference with the sponsor to communicate a concern regarding the recently received LA-01 inspectional findings and a decision to postpone the October 6, 2009 advisory committee meeting.

DISCUSSION POINTS:

The Agency noted that the inspectional (FDA DSI report) findings for the LA-01 study/Toronto site were received a few days ago. FDA noted that this report is lengthy and appears to raise questions regarding the completeness of the data from Study LA-01. FDA noted that Study LA-01 was the study with the largest randomized patient population within the portfolio of NDA studies (LA-01 was a randomized study of 71 subjects, a sample size which exceeds the sponsor's proposed main confirmatory study that consisted of 61 subjects). FDA also emphasized the importance of the endpoints assessed in Study LA-01 since there is a regulatory precedent for the use of these endpoints in a confirmatory study.

FDA explained that the upcoming advisory committee had been canceled. FDA noted that a thorough examination of the DSI report for Study LA-01 is essential along with verification of the completeness of supplied data from the study. FDA emphasized that this information could form a critical component of the NDA review and failure to thoroughly explain the DSI findings/Study LA-01 status at the advisory committee (ODAC) would likely compromise the usefulness of the advice from the committee members. FDA noted that proceeding without a thorough vetting of the Study LA-01 inspectional findings/data completeness, would likely necessitate a follow-up advisory committee.

FDA stated that the NDA review is ongoing, including the review of the LA-01 inspectional findings. FDA stated that further discussions are anticipated with the sponsor as soon as the inspectional findings can be reviewed. Due to the length of the inspectional report and complexity of the Study LA-01 issues, FDA could not place a time line upon this proposal for additional discussions. Nevertheless, FDA expressed a desire to work with the sponsor to thoroughly vet the Study LA-01 data.

In response to a copy of the inspectional report, FDA stated that efforts would be made to determine which parts of the report, if any, could be released through the Freedom of Information Act (FOIA).

The sponsor commented that they did not submit study LA-01 because it did not meet the Good Clinical Practices (GCP) standard. They stated that in the past, invalidated information was presented to EMEA. The sponsor stated that they really need to see the data that is contradictory with the information they have submitted.

FDA expressed a plan involving the site inspectors and FDA legal staff to help assess the Study LA-01 situation and to discern the information that can be shared with the sponsor. FDA will place a short announcement of the ODAC cancellation on the FDA website soon before publishing in the FR notice.

ACTION ITEMS:

- The Agency will place the ODAC cancellation notice on the FDA website followed by FR publication in the next few days.
- The Agency will check with FOIA to find out what information can be shared with the sponsor regarding the inspectional findings for Study LA-01/the Toronto clinical site.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
10/07/2009

MEMORANDUM OF TELECONFERENCE

Date: September 17, 2009

Time: 9:30-10 AM

Location: White Oak Bldg 22, Rm 2376

Application: NDA 21-825: Ferriprox® (deferiprone) 500 mg Tablet

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products:
Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader
George Shashaty, M.D., Medical Reviewer
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Office of Clinical Pharmacology:
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

And

External Constituent Attendees and Titles:

ApoPharma:
Fernando Tricta
Michael Spino
John Connelly

Cato Research:
Lynda Sutton
Vicki Gunto

The Division had a teleconference with the sponsor on September 14, 2009 to discuss the presentation plans for the upcoming Oncologic Drugs Advisory Committee (ODAC) scheduled on October 6, 2009. The Division set up a follow up teleconference to discuss the remaining items.

The Division stated that as discussed during the September 14th teleconference, we envision focusing on the following three items; to present and discuss the single clinical study (LA16-0102) as the sole adequate and well-controlled clinical trial proposed to verify efficacy, to

present and discuss the clinical meaningfulness of the Study LA 16-0102 primary endpoint (T2*) results, and to discuss deferiprone safety considerations.

The sponsor commented that they received the FDA ODAC briefing package yesterday and noticed that some items were not updated or factually not correct. They stated that some of them are significantly important and asked if they could forward them to the Division on Monday (September 21, 2009). For example, on page 52 of the briefing package, reference regarding the LA01 (Dr. Olivieri) and the allegations regarding liver fibrosis is not correct. They stated that the liver fibrosis was not mentioned to the company until Dr. Olivieri's participation in the trial was terminated, and not that her participation was terminated because of her statements of liver fibrosis. They stated that the trial was rather terminated due to non-compliance. They will provide supporting documentations for clarification.

The Division emphasized the intent to focus upon the clinical data and not the controversies between the sponsor and Dr. Olivieri. The Division noted that data integrity issues have been resolved for some products in the past and hopefully any issues that evolve for deferirpone can also be readily resolved.

The sponsor had the following questions regarding the FDA questions of the briefing package:

(b) (4)

The Division responded that we will go back and check the analysis for errors.

The sponsor commented that they will address these issues and their standings to the advisory committee.

(b) (4)

(b) (4)

(b) (4)

The Division stated that in the review of another iron chelator (deferasirox), it appeared that there was a decrease in LIC and serum ferritin; these decreases do not appear to have been demonstrated with deferiprone (although in LA03, it showed decreased level of serum ferritin and LIC). Up to the present time, LIC and serum ferritin have been the surrogate endpoints used to assess the main effects of iron chelating agents, and accelerated approval of deferasirox was based, in part, upon demonstration of favorable effects upon LIC and serum ferritin.

The Division noted that during the pre-NDA meeting in 2006, that it was made clear that ApoPharma appeared to have one possible adequate and well controlled clinical trial (LA16-0102). Other T2* studies, not conducted by the sponsor can be used for safety, but not for efficacy.

The sponsor asked if it is possible for the pre-print manuscript of Dr. Pennell to be forwarded to the advisory committee at this time or if they have to present it during the AC meeting. Division recommended that the sponsor consult with Nicole Vesely (Advisors and Consultants Staff). The Division noted that Dr. Pennell's paper contains data on the development of cardiac disease over time and compares that development to baseline T2* levels. The Division asked if there are clinical data that verify whether or not changes in T2* correlate directly to clinical benefit.

The sponsor responded that there is a paper by John Porter, et al. that followed patients for a 12 month period with IV deferoxamine for iron-induced cardiomyopathy, and that patients showed progressive improvements in T2 and LVEF. They will send the reference.*

On a difference note, they stated that they are planning to submit the proposed Risk Evaluation and Mitigation Strategy (REMS) by October 2, 2009.

ACTION ITEMS:

- The Division will clarify the FDA analyses of Study LA12-9907 as it pertains to the age-matched analysis.
- The sponsor will consult with Nicole Vesely to determine if the pre-print manuscript of Dr. Pennell can be forwarded to the advisory committee at this time or if the paper/data may be presented during the AC meeting.
- The sponsor will submit the proposed REMS by October 2, 2009.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
10/07/2009

MEMORANDUM OF TELECONFERENCE

Date: September 14, 2009

Time: 9:30-10 AM

Location: White Oak Bldg 22, Rm 2201

Application: NDA 21-825: Ferriprox® (deferiprone) 500 mg Tablet

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products
Rafel Rieves, M.D., Division Director
George Shashaty, M.D., Medical Reviewer
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK)
Joyce Weaver, Pharm.D., Risk Management Analyst

Center for Devices and Radiological Health (CDRH)
Sunder Rajan, Ph.D., Reviewer, Division of Physics (OSEL) & Division of Abdominal, Reproductive and Radiological Devices (ODE)

And

External Constituent Attendees and Titles:

ApoPharma:
Fernando Tricta
Michael Spino
John Connelly

Cato Research:
Lynda Sutton,
Vicki Gunto

The Division arranged the teleconference with the sponsor to discuss the presentation plans for the upcoming Oncologic Drugs Advisory Committee (ODAC) scheduled on October 6, 2009.

The Division stated that we started working on the presentations for the ODAC. The meeting will start with a brief introduction, followed by the sponsor's presentation (about 45 min), then FDA presentation (the clinical will form the bulk of the presentation). There will also be a

representative from Center for Devices and Radiological Health (CDRH) presenting on the MRI T2* in addition to the statistics presentation that will largely focus on the LA16-0102 study).

Division noted that FDA may grant accelerated marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Additional regulatory expectations also apply, as described in the CFR description of the accelerated approval process. The Division further noted that the sponsor has proposed only one adequate and well-controlled clinical study (LA16-0102) and this study has a primary surrogate endpoint (T2*). FDA noted that T2* has not previously been accepted as a clinically meaningful surrogate nor as a surrogate reasonably likely to predict clinical benefit; this lack of precedent presents challenges. Regulatory expectations are that the single study should provide robust data for safety and efficacy, and depending on the interpretation of the data, the regulatory options pertain to either full or accelerated approval or the need for additional data. The sponsor should provide data that changes in T2* are correlated with clinical benefit ("reasonably likely to predict clinical benefit"). FDA understands that the sponsor's supportive information that assesses the T2* as "reasonably likely to predict clinical benefit" largely comes from the pre-print of Dr. Pennell's manuscript of 652 patients.

The sponsor responded that they plan to present the currently supplied pre-print of Dr. Pennell's manuscript (scheduled to be posted on October 2, 2009) as the main supportive data for use of T2 as a surrogate endpoint reasonably likely to predict clinical benefit, the LA16-0102 study and the observational studies. They stated they would share slides.*

The Division noted that the major confirmatory data supporting approval of a NDA cannot be derived from observational studies. The Division further noted that the sponsor's recent submission (from a single analysis of Dr. Pennell's) states that an increase of 1 msec in T2* in a person with a baseline T2* of 8-10 msec corresponds to 39.6 % decrease in cardiac events, but that the sponsor did not provide prospective information that an increase of 1 msec in T2* results in reduction of cardiac events. To help establish the usefulness of T2* as an endpoint, the sponsor needs to provide data that can form the basis of understanding that if a patient has an XX msec increase in T2*, this degree of increase in msec will predict a lessening of cardiac events. For example, the sponsor should provide prospective data that compares deferiprone with placebo or an active comparator and design the study(ies) to show that decreases in clinical events is predicted by improvements of T2* (i.e., need corroborative information that the surrogate predicts clinical efficacy).

The sponsor responded that in order to perform this type of a prospective study, they would need a couple of hundred of patients followed for five years, and that it would be impractical. They commented that they conceptually align T2 with the cardiac risk assessments afforded by cholesterol values.*

They asked if a post-marketing study would be necessary if this NDA is granted accelerated approval and FDA confirmed that the accelerated approval pathway necessitates the submission of post-marketing clinical data that establish efficacy, based upon the assessment of clinically meaningful endpoints. They further stated that multiple publications describe deferiprone benefits. The sponsor will send the publications again.

The Division suggested that for additional pre-approval or post-marketing studies, the sponsor should consider the development of blinded, well-controlled studies that compare deferiprone with deferasirox (since both are for oral administration) and construct endpoints as appropriate.

In interest of time, the Division noted that we will end the teleconference and will schedule a follow up teleconference to discuss this issue further if needed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
09/16/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21825

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

ApoPharma Inc.
c/o CATO Research Ltd.
4364 South Alston Avenue
Durham, NC 27713-2220

ATTENTION: Lynda Sutton
Chief Regulatory Officer, Cato Research Ltd.

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deferiprone Tablets, 500 mg.

We also refer to your June 15, 2009, correspondence, received June 15, 2009, requesting reconsideration of your proposed proprietary name, Ferriprox. We have completed our review of the proposed proprietary name, Ferriprox and have concluded that it is acceptable.

The proposed proprietary name, Ferriprox, will be re-reviewed 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 June 15, 2009 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 Catherine Carr, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2311. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hyon-Zu Lee at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

CAROL A HOLQUIST
09/11/2009

MEMORANDUM OF TELECONFERENCE

Date: August 17, 2009

Time: 4:15 p.m.-4:45p.m. Bldg 22, Rm 2157

Application: NDA 21-825 Ferriprox (deferiprone)

Between:
DMIHP
Kathy Robie-Suh, M.D., Ph.D.; Medical Team Leader-Hematology, DMIHP
George Shashaty, M.D., Medical Officer, DMIHP

And

CATO
Lynda Sutton
Vicki Gunto
Evan Richardson

ApoPharma
Dian Shaw
Kai Mardy
Lopa Bandyopadhyay
Fernando Tricta

The clinical review team requested this teleconference with ApoPharma to obtain clarification on some of the information ApoPharma sent to the Agency on Friday, August 14, 2009 in response to an information request from the Division sent July 31, 2009.

Dr. Shashaty explained that the review team is trying to understand how assignments of NYHA class were made for patients in Study LA12-9907. Dr. Shashaty commented that in one of the questions to the sponsor the pertinent section of the submission was misidentified and should have been Section 12.2.7 which pertained to a table giving Patient Listing of Cardiac Assessment Results. He explained that for a number of the patients it was not clear based on the information in the table how the sponsor arrived at the NYHA class assignment indicated in the table. Dr. Shashaty cited several examples from the table in which it appeared that the NYHA classification was based on a decrement in left ventricular shortening fraction or left ventricular ejection fraction. These changes appeared to be small and were sometimes transient. In a previous communication the sponsor had indicated that the cardiologist who assigned the classification did not actually see the patients but reviewed clinical records. In the most recent communication the sponsor indicated that the assignment was made based on clinical assessment. Dr. Shashaty requested clarification as to how this was done.

ApoPharma responded that from 1995-2001 patients were seen locally by a cardiologist yearly. For the assessment for EMEA, there was a separate cardiologist who (blinded) reviewed cardiology charts of the patients and assigned NYHA class each year. That assessment took into account chart notes about symptomatology as well as measurements.

Dr. Shashaty stated that he was particularly interested in seeing the supporting information for NYHA assignment for deferiprone patients number: 42, 48, 55, 58, 57, 80, 84, 96, and 170 and for deferoxamine patients number: 1, 8, 14, 15, 16, 19, 20, 21, 22, 27, 30, 33, 40, 44, 50, 54, 61, 63, 76, 77, 101, 122, 142, 154, and 171. ApoPharma said they would contact Italy to see if they could get information to support the congestive heart failure diagnosis and NYHA class in these patients. Dr. Robie Suh commented that it would be very helpful to have the cardiologist's reports for all of the patients in the study if these could be obtained.

ApoPharma indicated that they better understood the question and would try to get the requested information. They will let us know an estimated time to obtain the additional information.

The teleconference was concluded.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21825	ORIG 1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

KATHY M ROBIE SUH
08/20/2009

MEMORANDUM OF TELECONFERENCE

Date: August 14, 2009

Time: 1:30-2 PM

Location: White Oak Bldg 22, Rm 2327

Application: NDA 21-825: Ferriprox® (deferiprone) 500 mg Tablet

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products
Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
George Shashaty, M.D., Medical Reviewer
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Center for Devices and Radiological Health (CDRH)
Sunder Rajan, Ph.D., Reviewer, Division of Physics (OSEL) & Division of Abdominal, Reproductive and Radiological Devices (ODE)

And

External Constituent Attendees and Titles:

ApoPharma:
Fernando Tricta
Michael Spino
John Connelly

Cato Research:
Lynda Sutton,
Allen Cato
Vicki Gunto

Consultant:
Dudley Pennell

The Agency set up the teleconference with the sponsor to prepare for the upcoming Oncologic Drugs Advisory Committee (ODAC) scheduled on October 6, 2009.

The Agency emailed the attachment (below) on August 13, 2009 and arranged the teleconference for the sponsor to ask any questions that they might have regarding the request.

The Agency stated that we need to be sure that we are in line with the data (changes of T2*, ejection fraction and clinical benefit outcome), and hope that the sponsor can provide slides and data that will help our preparation for the ODAC. The Agency asked if the sponsor has any questions to our request.

The sponsor commented that Dr. Pennell currently has a paper that is in process for publication (that addresses question number 1) and that they do not want to jeopardize the embargo situation for that publication. They stated that it would be ideal if its key data could be presented to ODAC and be included in the briefing package.

The Agency noted that there was a similar situation before and advised that Dr. Pennell get in touch with the journal editor. FDA noted that in past experiences, journal editors have been very cooperative and understanding. If the paper contains a dataset that is relevant or essential for the application, it would be beneficial to have the information supplied to the NDA and to our advisors. Also, the sponsor should contact Nicole Vesely (Advisors and Consultants Staff) regarding the briefing package and any public disclosure issues.

Regarding question number 3, the sponsor stated that brain was not measured and that when T2 moves more to normal range (>20 msec), both accuracy and reproducibility greatly decreases. They stated that the equipment manufacturer makes regular 3 months assessments for quality assurance. Regarding sensitivity to shimming, they stated that iron loading is the dominant effect and shimming has trivial effects in the MR measurement of T2*.*

The Agency stated that in LA16-0102, LVEF was measured by NMR and echocardiography. The Agency needs to know the relationship of T2* and cardiac function measurements. To thoroughly support the use of the T2* endpoint, the sponsor needs to provide robust prospective data that support a predictive relationship between an increase of T2* and clinical benefit.

The teleconference concluded.

ACTION ITEMS:

- The sponsor will respond to our information request (attached below) by August 20, 2009.

- Dr. Pennell will get in touch with the journal editor to discuss if the pre-print manuscript can be submitted to the Division, and when the paper will be published. The sponsor will contact Nicole Vesely to discuss if the paper can be included in the briefing package and public disclosure issue.

August 13, 2009

We request succinct responses to the questions listed below. Please respond as soon as possible, preferably within a week.

1. What data (epidemiological, clinical trial, etc) are available to support the contention that changes in cardiac iron content as measured by MRI T2* are reasonably likely to predict clinical effects of iron chelation therapy in patients with transfusional hemosiderosis?

a. In your response, develop a slide that succinctly lists the main data sources (e.g., 2 to 4 bullets) and supply a text that specifically identifies the data source location in the NDA.

b. Additionally, please comment upon the extent of data specifically available for patients with transfusional hemosiderosis versus normal subjects and versus patients with other conditions.

2. What data (epidemiological, clinical trial, etc.) are available to support the contention that the extent of changes (during iron chelation therapy or disease progression) in cardiac ejection fraction are reasonably likely to predict clinical effects of therapy in patients with transfusional hemosiderosis?

a. In your response, develop a slide that succinctly lists the main data sources (e.g., 2 to 4 bullets) and supply a text that specifically identifies the data source location in the NDA.

b. Additionally, please comment upon the extent of data specifically available for patients with transfusional hemosiderosis versus normal subjects and versus patients with other conditions.

3. In Study 16-0102, both study groups (deferiprone and deferoxamine) generally had increases in T2* values over the 12 month observation period. These changes could reflect drug effects or they could reflect changes in the T2* measurement technology. We understand imaging technology changes rapidly (new software, new operators, new positioning, etc) and we need data to help verify whether changes in any imaging assay methodology may have impacted the T2* measurements. Please supply these data; we specifically suggest you supply:

a. For each patient T2* measurements for iron content within an organ that generally should not contain much iron (for example, the brain), at study entry and over the clinical study period. Stability of these values may help verify stability of the imaging assay system.

b. Procedural log verification of the use of phantoms to qualify the imaging assay methodology throughout the study conduct.

c. A description of any alterations in imaging assay procedures, such as new software, new imaging staff or any other aspects of image acquisition/image assessment that may alter T2* values.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
09/16/2009

MEMORANDUM OF TELECONFERENCE

Date: August 12, 2009

Time: 8:30-9 AM

Location: White Oak Bldg 22, Rm 2376

Application: NDA 21-825: Deferiprone 500 mg film-coated tablet.

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products
Rafel Rieves, M.D., Division Director
George Shashaty, M.D., Medical Reviewer
Ira Krefting, M.D., Deputy Director for Safety
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK)
Claudia Karwoski, Pharm.D., Division Director
Joyce Weaver, Pharm.D., Risk Management Analyst

And

External Constituent Attendees and Titles:

ApoPharma:
Fernando Tricta
Gerry Belgraver
Michael Spino

Cato Research:
Lynda Sutton,
Allen Cato
Vicki Gunto

The Agency arranged the teleconference with the sponsor to communicate that we envision the need for submission of a Risk Evaluation and Mitigation Strategy (REMS) for consideration with this application.

The Agency noted that we specifically envision a need for a REMS proposal with Elements to Assure Safe Use (ETASU) for deferiprone. This does not mean that we have concluded the application has a favorable benefit/risk profile for the drug or that we have finished our review. Instead, we are providing this information based upon our preliminary observations and our

intent to try to facilitate the review in the event a REMS is necessary to proceed along a favorable pathway.

The preparation of final REMS document requires considerable time and logistical procedures. It would be wise for the sponsor to start preparing for a REMS document considering the PDUFA due date of November 30, 2009. Anticipated necessary REMS components are: a Medication Guide, Elements to Assure Safe Use, An Implementation System, a Timetable for Submission of Assessments, Information needed for Assessment and a Communication Plan. We anticipate that the ETASU would incorporate a requirement for enforced laboratory values monitoring to be linked to drug accessibility.

We will send a copy of the formatting template that describes the REMS and supporting document to the sponsor. Additionally, there are examples of REMS documents available on the FDA website for hematology drugs such as Nplate and Promacta. The sponsor should submit a draft of the proposed REMS and a draft REMS Supporting Document as soon as possible. The Agency also advised that it would be wise for the sponsor to be prepared to discuss a proposed risk management plan at the upcoming Oncologic Drugs Advisory Committee (ODAC).

The sponsor responded that they would try to include as many REMS components in the upcoming AC presentation.

The teleconference concluded.

Post-meeting actions:

The Agency emailed the REMS and supporting document template (attached below) to the sponsor on August 12, 2009 after the teleconference.

REMS TEMPLATE
April 10, 2009-*REVISED*

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:
List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21825	ORIG 1		FERRIPROX (DEFERIPRONE)

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

/s/

HYON-ZU Z LEE
08/14/2009

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Wednesday, August 12, 2009 12:13 PM
To: 'Lynda Sutton'
Subject: NDA 21-825 deferiprone
Attachments: REMS Template A B (Revised 5 18 09).doc

Ms. Sutton,

As a follow up of today's teleconference, see attached the REMS template. Please provide a timeline when you are planning to submit your REMS draft proposal.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:
List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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

/s/

HYON-ZU Z LEE
08/12/2009

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, July 31, 2009 2:13 PM
To: 'Lynda Sutton'
Subject: NDA 21-825 deferiprone

Ms. Sutton,

Please refer to your NDA 21-825 submitted on January 29, 2009 for deferiprone tablets.

We have the following clinical information request:

- On January 31, 2006, you established an expert panel to evaluate the mechanism of the development of, and the approaches to reducing the occurrence of, agranulocytosis due to deferiprone therapy. Provide all information related to that panel, including but not limited to dates and minutes of meetings, reports reviewed, investigations undertaken, conclusions drawn and actions recommended.

- Study LA 16-0102 completed the last patient on October 13, 2004. For the period following completion of the study through the end of June, 2009, provide the following information for each enrolled subject in both the deferiprone and the deferoxamine treated arms:
  - Alive or dead
  - Development of any cardiac disease. If cardiac disease has been diagnosed, provide specifics of the problem and the method of diagnosis
  - Chelation therapy since termination of subject from the study, including adverse reactions, discontinuations, etc.
  - All subsequent investigative observations (with dates thereof), including but not limited to serum ferritin levels, liver iron studies, left ventricular ejection fractions, left ventricular shortening fractions, and MRI T2*
  - Other medical problems that have occurred since the end of participation in the study

- For Study LA 12-9907:
  - In Section 12.7.7.2, it appears that a number of subjects were declared by the cardiologist to be classified as NYHA I on the basis of a minimal and often transitory decrease in left ventricular shortening fraction (and less often of left ventricular ejection fraction) in the absence of any cardiac symptomatology or other supportive data. Provide a statement that either concurs or disagrees with this understanding.
  - If your statement concurs with this understanding, provide evidence that such decrements in the shortening fraction and the ejection fraction are related to clinical outcomes.
  - Since the determination of shortening fraction and ejection fraction are subject to quantification by the observer, provide the mean and standard deviations for the person(s) readings of these studies both when they are in the normal range as well as for those below the normal range. Also provide evidence that these means and standard deviations did not change during the period in which the patients were evaluated.

- In PSUR 3 (August, 2000 to February, 2001), you indicate that Dr. Robert Grady at Cornell was conducting an iron balance study in patients treated with deferiprone. Provide the protocol and all data from that study, including a complete study report, if available.

Please respond by August 12, 2009.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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

/s/

HYON-ZU Z LEE
07/31/2009

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: Division of Physics (DP)

Mail Code: HF_-
Consulting Reviewer Name: Sunder Rajan
Building/Room #: WO 62/Rm 1113
Phone #: 301-796-4194
Fax #:
Email Address: Sunder.Rajan@fda hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: Division of Medical Imaging and Hematology Products
Mail Code: HFD-160
Requesting Reviewer Name: George Shashaty
Building/Room #: WO 22/ Rm 2185
Phone#: 301-796-1458
Fax #:
Email Address: George.Shashaty@fda hhs.gov
RPM/CSO Name and Mail Code: Hyon-Zu Lee
Requesting Reviewer's Concurring Supervisor's Name: Rafel Rieves

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 10, 2009

Requested Completion Date: **July 31, 2009 (negotiable)**

Submission/Application Number: 21-825

Submission Type: NDA

Type of Product: ☐ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☒ Not a combination product

Submission Receipt Date: January 29, 2009

Official Submission Due Date: N/A

Name of Product: Deferiprone

Name of Firm: ApoPharma

Intended Use: Deferiprone is an iron chelator indicated for:

•the treatment of iron overload in patients with transfusion-dependent thalassemia.
•the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
Please see email (and attachment) dated July 8, 2009.

Documents to be returned to Requesting Reviewer? π Yes ☐ π No ☒

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review ☒ π Collaborative Review ☐

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

/s/

Hyon Z Lee

7/10/2009 01:25:29 PM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Thursday, July 02, 2009 9:28 AM
To: 'Lynda Sutton'
Subject: NDA 21-825 deferiprone: statistical comments and information requests
Importance: High

Ms. Sutton,

As discussed earlier, please see below our statistical comments and information requests. Please respond by July 9, 2009.

1 As per your submitted information in NDA 21-825, the statistical methods pre-specified in the protocol and statistical analysis plan for the study LA16-0102 were analysis of variance (ANOVA) for the endpoints of change in MRI T2* from baseline at month 12 and change in cardiac function (LVEF, mass, etc) and Chi-square test or Fisher's Exact test to compare the incidences between the two groups. However, the analyses presented in the study report of your submission were based on log-transformation of the MRI T2*. Please clarify whether your analyses are post-hoc analyses and if so, provide a justification for these analyses. Please clearly state the results of the prospectively defined (from the statistical analytical plan) primary endpoint result; we need to have a clear, mutual understanding of the prospectively defined primary endpoint result.

2 We are concerned that randomization employed in your study LA16-0102 did not achieve balance between the two treatment groups with respect to important covariates such as splenectomy status, Hepatitis C status and serum ferritin concentrations at baseline. You should perform appropriate analyses that take into account these imbalances.

3 We have examined your data in study LA16-0102 on MRI T2* for departures from normality using various parametric and non-parametric tests. These tests showed that MRI T2* or the log-transformed MRI T2* data at the baseline were not normally distributed. This was also true for the primary efficacy evaluation variable – difference in MRI T2* evaluations at month 12 (or 6) from baseline. This lack of normality potentially jeopardizes the validity of your analysis methods and renders the results un-interpretable. Although no other analytical methods were pre-specified in your protocol or SAP for the situation of non-normal data, perform and submit proper analyses of your data using appropriate transformations and/or methods that do not assume normality (say, non-parametric methods) and that account for the baseline imbalances (see comments 2 above).

4 For Study LA12-9907, the data for survival analysis has multiple records per patient and lacks an indicator variable (or censor variable) regarding the occurrence of a cardiac event. Provide these data in one record per patient that should include unique subject ID, age at baseline, start age of chelation therapy, NYHA class at baseline (Year=0), Year of first cardiac event, Indicator (censor) variable (occurrence of cardiac event 0=Yes, 1=No), NYHA class at censoring time, Subgroup1 (0=no, 1=yes), Subgroup2 (0=no, 1=yes), Information on covariates at baseline, information on important covariates (e.g., Serum Ferritin Concentration, Hepatitis C Status, Transfusional Iron Input, urinary iron excretion, hepatic iron concentration), and any other information useful in evaluating this study in this one master data file. Also include time on chelation therapy up to the baseline and total time on chelation up to the end of study in years.

5 It appears that there are many confounding factors impacting cardiac disease and survival in study LA12-9907 due to its non-randomized study design. One method to assess the impact of several observed covariates on treatment effects in the absence of randomization is the use of propensity score, defined as the conditional probability of being treated given the covariates. An excellent reference is a paper by Ralph B. D'Agostino, "Tutorial in Biostatistics, Propensity Score Methods for Bias Reduction in the Comparison of a Treatment to a Non-randomized Control Group", Statistics in Medicine, vol. 17(1998), pp 2265-2281. A list of covariates that should be included in the model are - Age at baseline, Age at the start of chelation therapy, Serum Ferritin Concentration, Hepatitis C Status, Transfusional Iron Input, urinary iron excretion, hepatic iron concentration. You should feel free to add to this list. Perform and submit analysis based on propensity scores for study LA 12-9907.

6 We recommend that you submit the computer programs you generate to perform the various

analyses suggested in the comments 1-5 above. This will facilitate a fast and thorough review of the information in this NDA.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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

/s/

Hyon Z Lee
7/2/2009 09:54:53 AM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Thursday, August 13, 2009 5:26 PM
To: 'Lynda Sutton'
Cc: Evan Richardson; Vicki Gunto
Subject: RE: NDA 21-825 deferiprone: Teleconference for 14 Aug 09
Attachments: 21825 Requests.8.13.09.doc

Linda,

The time of the teleconference has moved to 1:30-2 pm (EST) tomorrow (August 14, 2009). Please see attached the discussion points for the teleconference.

Thank you,
Hyon-Zu

From: Lynda Sutton [mailto:lsutton@cato.com]
Sent: Thursday, August 13, 2009 4:26 PM
To: Lee, Hyon-Zu
Cc: Evan Richardson; Vicki Gunto
Subject: RE: NDA 21-825 deferiprone: Teleconference for 14 Aug 09
Importance: High

Good afternoon,

Would it be possible to change the time of the call to 1:30 pm? Several participants from ApoPharma will not be available at 11:30 am. If not, a limited number of participants can be available for the call at 11:30 am, but may not be able to address questions raised by the Division. The following call-in information can be used for the 11:30 or the 1:30 pm call tomorrow:

US/Canada dial-in number: (b) (4)
International dial-in-number: (b) (4)
Passcode: (b) (4)

The call starts as soon as the first participant enters a passcode followed by the # sign.

For assistance with audio or other problems, please press * 0 and an operator will come on the line.
To mute, press * 6. To take off mute, press * 6 again.

Please let me know if a change of time is possible. If you would like to call my cell phone to discuss tonight, my number is (b) (6) Thank you for your help.

Lynda Sutton
US Agent for NDA 21-825

This electronic communication and any documents, files or previous messages attached to it may

August 13, 2009

We request succinct responses to the questions listed below. Please respond as soon as possible, preferably within a week.

1. What data (epidemiological, clinical trial, etc) are available to support the contention that changes in cardiac iron content as measured by MRI T2* are reasonably likely to predict clinical effects of iron chelation therapy in patients with transfusional hemosiderosis?

   a. In your response, develop a slide that succinctly lists the main data sources (e.g., 2 to 4 bullets) and supply a text that specifically identifies the data source location in the NDA.

   b. Additionally, please comment upon the extent of data specifically available for patients with transfusional hemosiderosis versus normal subjects and versus patients with other conditions.

2. What data are (epidemiological, clinical trial, etc) are available to support the contention that the extent of changes (during iron chelation therapy or disease progression) in cardiac ejection fraction are reasonably likely to predict clinical effects of therapy in patients with transfusional hemosiderosis?

   a. In your response, develop a slide that succinctly lists the main data sources (e.g., 2 to 4 bullets) and supply a text that specifically identifies the data source location in the NDA.

   b. Additionally, please comment upon the extent of data specifically available for patients with transfusional hemosiderosis versus normal subjects and versus patients with other conditions.

3. In Study 16-0102, both study groups (deferiprone and deferoxamine) generally had increases in T2* values over the 12 month observation period. These changes could reflect drug effects or they could reflect changes in the T2* measurement technology. We understand imaging technology changes rapidly (new software, new operators, new positioning, etc) and we need data to help verify whether changes in any imaging assay methodology may have impacted the T2* measurements. Please supply these data; we specifically suggest you supply:

   a. For each patient T2* measurements for iron content within an organ that generally should not contain much iron (for example, the brain), at study entry and over the clinical study period. Stability of these values may help verify stability of the imaging assay system.

   b. Procedural log verification of the use of phantoms to qualify the imaging assay methodology throughout the study conduct.

c. A description of any alterations in imaging assay procedures, such as new software, new imaging staff or any other aspects of image acquisition/image assessment that may alter T2* values.

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

/s/

HYON-ZU Z LEE
08/13/2009

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Wednesday, May 27, 2009 10:34 AM
To: 'Lynda Sutton'
Subject: NDA 21-825 deferiprone
Follow Up Flag: Follow up
Flag Status: Blue

Lynda,

I have received your voicemail. Please see our responses:

- Yes, we have reviewed your submission of May 6 (including both the responses to our filing comments, and your comments regarding questions raised by us in the orientation meeting of April 13, 2009). Some of the responses relate to the questions in this latest information request. If you believe that those responses are pertinent to the questions in the information request, please include them in your responses to our questions even if they appear to be reduplicative.

- An Image Review Charter is a comprehensive, pre-specified image protocol to verify that the images are reproducible and that the reads are unbiased and reliable. This should include pre-specified:

  a. Quality control of the cameras (machine drift, reproducibility of the images over time)
  b. Details of image acquisition (timing, MRI parameters, etc)
  c. Procedure for image reads (de identification of the MRI data, blinding of reads, randomization of sequence, selection of an ROI, independence of the reader)
  d. Procedure for identifying the variability of the reads (inter reader/intra reader)

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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

/s/

Hyon Z Lee
5/29/2009 08:55:15 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825

INFORMATION REQUEST LETTER

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA)-Pilot 1 program, for deferiprone 500 mg film-coated tablet.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response within 21 days of receipt of this letter in order to continue our evaluation of your NDA.

For Study 16/0102:

- Provide analyses of the relationships between the measure of MRI T2* and MRI LVEF, ECHO LVEF and ECHO LVSF. Analyses should include the degree of correlation with standard deviations and confidence intervals and timed correlations (at baseline, 6 and 12 months of the trial).

- Provide data that correlate MRI T2* measurements with the results of quantitative chemical measurements of iron concentration in the heart.

- You have indicated that there is a difference in cardiac MRI T2* of 2.3 ± 2.2 ms in patients treated with deferiprone for 1 year. Provide evidence that this change in MRI T2* indicates a meaningful effect of deferiprone on clinical outcomes of thalassemia patients with iron overload.

- Provide data that show that measurement of MRI T2* allows for the diagnosis of preclinical iron-induced cardiac abnormalities that are a predictor of the development of clinical heart disease.

- Provide the Image Review Charter for the cardiac T2* portion of the study that details the procedures used to acquire, display and interpret the images and to transfer the data for analysis. The charter should include a procedure for image acquisition; quality control; de-identification of data; blinding of reads; randomization of sequence; selection of an ROI; independence of the reader; and, variability of reads.

- Although the study sites were qualified initially for the performance of MRI T2*, there are no listed procedures for verification of the reproducibility of the images over the time of the study (e.g., machine drift).

- Provide the charter for the blinded readings of the ECHO LVEF and LVSF.

- One hundred and sixty (160) patients were screened in order to enroll 61 patients on the trial. Eleven (11%) percent of screened persons were excluded because of an MRI T2* of less than 8 ms and 2% were excluded because of a diminished LVEF. What were the MRI T2* measurements in the patients with a diminished LVEF. Also, provide followup information (mortality, development of cardiac disease, etc) on the patients who were not enrolled on the trial because of a diminished MRI T2* measurement or for a diminished LVEF.

For Study 12/9907:

- For each patient who was begun on deferiprone, provide the reason as to why he/she was converted from deferoxamine at the time of commencement of the observation period.

- Provide the number of patients who were begun on deferiprone de novo before receiving any deferoxamine.

- Explain how the cardiologist was blinded to treatment assignment for each examined patient. It would appear that careful history and physical examination (needle marks, skin irritation, local hematoma) of each patient would easily allow the differentiation of those patients receiving deferoxamine from those being orally treated with deferiprone.

- It appears that for many patients, the diagnosis of clinical heart disease was based on a LVEF or LVSF that fell below some arbitrary value. Provide the measurements used by the cardiologist to calculate the LVEF and the LVSF.

- It appears that symptomatic heart disease was present in only a minority of patients. For these symptomatic patients, provide a separate analysis and discussion of demographics, treatment and outcomes.

- There were no differences from baseline to end of study in LVEF (70.9 ±7.2 to 69.4 ±6.6 and 69.0 ±7.0 to 69.2 ±8.4) or LVSF (37.0 ±6.1 to 36.8 ±4.2 and 36.3 ±6.6 to 35.4 ±5.1) for patients assigned to deferiprone and deferoxamine, respectively. Provide an analysis for the LVEF and the LVSF at the end of 1 year of the study. If there are no differences at the end of 1 year for Study LA/12/9907, provide your explanation for this in light of the differences observed in Study LA16/0102.

- Sixteen patients were excluded from analysis because they did not have at least 4 years of chelation therapy during the observation period. For these patients, provide the following:

    - The number receiving deferiprone and the number receiving deferoxamine with the number of days of treatment received during the observation period.

    - The number of patients in each arm not receiving therapy because of adverse reactions.

    - Analyses of demographic characteristics, primary and secondary efficacy endpoints, and safety evaluations for these patients.

For Other Submitted Studies:

- For Study LA/01, provide your own review of the liver biopsy data (which you alluded to in the briefing meeting of April 13, 2009) that you believe contradicts the conclusions of the primary investigator that led to a publication that indicated refractoriness to therapy and excess hepatic fibrosis in patients treated with deferiprone compared to patients treated with deferoxamine.

- Patients described in Study LA 12/9907, the Borgna-Pignatti report and Study LA 17/9701 appear to have a commonality of institutions from which they were selected. It appears, therefore, that some of the patients are listed as having been participants in more than one of the reports and may be duplicated. Provide a list of patients from the three cited studies who were enrolled in two of the studies, and of patients who were enrolled in all three of the studies.

Other Requests:

- In the Clinical Overview Section (Module 2, Section 2.5), on page 21, you state that "Cardiac MRI T2*… has been approved with a CE mark in the EU for use as a Class I Medical Device, and has been approved in principle by the FDA". Explain what a "CE mark" is and indicate its significance in regard to medical management. Explain the exact status of the cardiac T2* methodology vis a vis the FDA.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Kyong Kang
5/19/2009 11:11:10 AM

MEMORANDUM OF TELECONFERENCE

MEETING DATE:	April 13, 2009
TIME:	2:00 PM – 3:30 PM (EST)
LOCATION:	Conference Room 1415 (White Oak)
APPLICATION:	NDA 21-825
DRUG NAME:	Deferiprone 500 mg Film-Coated Tablets
TYPE OF MEETING:	Applicant Orientation Meeting

MEETING CHAIR: Rafel Rieves, M.D.

FDA ATTENDEES:

Richard Pazdur, M.D., Office Director
Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
George Shashaty, M.D., Medical Reviewer
Mark Levenson, Ph.D., Acting Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Paul Hepp, Pharm.D., Clinical Pharmacology Reviewer
Mike Adams, Ph.D., CMC Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager
Ira Krefting, M.D., Associate Director for Safety
Anthony Orencia, M.D., DSI Reviewer, OC
Timothy Lape, Pharm.D., Safety Reviewer, OSE
Joseph Kaminski, M.D., Medical Reviewer
Diane Leaman, Regulatory Project Manager for Safety
Kassa Ayalew, M.D., Medical Team Leader

Robert Kane, M.D., Associate Director for Safety, DDOP
Edvardas Kaminskas, M.D., Medical Reviewer, DDOP
Albert Deisseroth, M.D., Medical Reviewer, DDOP

EXTERNAL CONSTITUENT ATTENDEES:

ApoPharma Inc.:

Lopa Bandyopadhyay, Manager, Regulatory Affairs
John Connelly, Ph.D., Director, Global Project Management, Apotex Inc.
Elizabeth Gill, Associate Director, Clinical Data Management
Elisabeth Kovacs, Director, Analytical Operations, Apotex Inc.
Kai Mardy, Project Leader, Regulatory Affairs
Michael Spino, President
Fernando Tricta, M.D., V.P., Medical Affairs
Yu Chung Tsang, CSO, Biopharmaceutics, Biostatistics

Consultants:

Dudley Pennell, M.D., Professor of Cardiology, Imperial College, London
Allen Cato, President, Cato Research Ltd.
Vicki Gunto, Director of Regulatory Affairs, Cato Research Ltd.
Evan Richardson, Regulatory Associate, Cato Research Ltd.
Jack Snyder, M.D., Clinical Research Physician, Cato Research Ltd.
Lynda Sutton, Chief Regulatory Officer, Cato Research Ltd.

FERRIPROX® (deferiprone, DFP)
NDA 21-825

Application Orientation Meeting

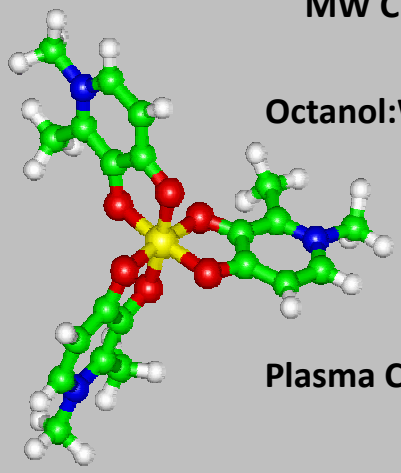
Fernando Tricta, M.D.
V.P., Medical Affairs
ApoPharma Inc.

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Presentation Outline

- Presentation of Compound
- Drug Development History
- Clinical and Statistical Reviewable Unit
  - Integrated Summary of Safety
  - Integrated Summary of Efficacy
- 120-Day Safety Report

FERRIPROX® (deferiprone, DFP) – NDA 21-825



Molecular Weight: 139 g/mol

MW Chelator-Iron Complex: 470 g/mol

Charge of Chelator: Neutral

Octanol:Water partition coefficient : 0.18

Protein Binding: < 10%

Volume of Distribution: Large

Route: Oral

Oral Absorption: 45 minutes

Plasma Clearance ($T_{1/2}$): 53 – 166 minutes

Iron Excretion: 80% renal

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Comparison of Iron Chelators

	deferiprone	deferasirox	deferoxamine
Molecular Weight	139	373	560
Partition Coefficient	0.18	6.3	0.02
Protein Binding	<10%	99% (albumin)	<10%
Charge of Chelator	neutral	negative	positive

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Comparison of Iron Chelators

	deferiprone	deferasirox	deferoxamine
Molecular Weight	139	373	560
Par Coef			
Pr Binding		(albumin)	
Charge of Chelator	neutral	negative	positive

The **unique physical chemical properties of deferiprone** allow rapid accessibility to intracellular labile iron

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History I

1984	Synthesized and patented (use) by academics; little interest for commercial development
1987	The first publication on the efficacy (rats)
1987	First publications in humans (MDS patients)
1989	First episode of agranulocytosis (Diamond Blackfan patient)
1991	Ciba-Geigy commits to its development
1993	Ciba-Geigy discontinues development
1993	Objection by patients and physicians (Lancet 1993)
1993	Investigators meeting with FDA: GMP Sponsor Required
1993	Apotex commits to evaluate safety and efficacy

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History II

1993 - 1996	**LA03**: Compassionate use (N=25)
1993 - 1998	**LA01**: Randomized, active controlled (N =71)
1995 - 2002	**LA02/06** : Uncontrolled, primarily safety (N=187)
1996 - Ongoing	**LA04/06B**: Uncontrolled, compassionate-use (N=96)
1997 - 2000	**LA17**: Multicenter, uncontrolled, active drug surveillance study (N=532)
1998 - 2001	**LA08**: Randomized, parallel, active-controlled (N=60)

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History II

1993 1996	**LA03**: Compassionate use (N=25)
1993 - 1998	**LA01**: Randomized active controlled (N =71)
1995 -	187)
1996 -	e
1997 -	g
	surveillance study (N=532)
1998 2001	**LA08**: Randomized parallel, active-controlled (N=60)

1999: Approved by the EMEA
(exceptional circumstances with commitments for follow up studies)

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History II

1999 - 2000	**LA10**: Single crossover, cytogenetics (N=20)
2000 - 2000	**LA14**: Pharmacokinetics (N=6)
2000 - 2000	**LA15**: Uncontrolled (N=29)
2000 - 2002	**LA11**: Uncontrolled (N=24)
2000 - 2001	**LA12**: Prospectively designed, retrospective and prospective data, parallel, longitudinal, active-controlled (N=129)

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History II

1999 - 2000	**LA10**: Single crossover, cytogenetics (N=20)
2000 - 2000	**LA14**: Pharmacokinetics (N=6)

2002: EMEA makes indication less restrictive

- Treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate

FERRIPROX® (deferiprone DFP) – NDA 21-825

Deferiprone Development – History II

1999 - 2000 **LA10**: Single crossover, cytogenetics (N=20)

Development of accurate/reproducible/noninvasive method for assessment of cardiac iron concentration

No clinically useful relationship between serum ferritin or liver iron concentration and cardiac T2*

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History II

2003 - 2004	**LA16**: Multicenter, randomized, active control (N=61)
2004 - 2004	**LA20**: Open-label, single-dose, three-way crossover study (N=15)
2004 - 2005	**Borgna-Pignatti et al**.: Natural history (N=526)
2005 - 2005	**LA21**: Open label, single-dose, randomized, two-way crossover (N=42)

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – as of 31 AUG 2006

- 517 subjects in clinical trials / compassionate use / active controlled program (57 healthy volunteers). Does not include LA17 and Borgna-Pignatti studies.
- Approved in 49 countries
- Post-marketing exposure = 14,875 patient-years
- PubMed:
  - 477 publications
  - 75 clinical trials (15 randomized)
  - 78 reviews

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Deferiprone Development – History II

2009

Proposed Indication:

▪The treatment of iron overload in patients with transfusion-dependent thalassemia.

▪The treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

(b) (4)

NDA 21-825
FERRIPROX® (deferiprone, DFP)

Integrated Summary of Safety
Integrated Summary of Efficacy

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Data Pools

Pool 1: Pivotal studies (LA12 & LA16)
Efficacy endpoints: cardiac iron concentration, cardiac function, cardiac morbidity & survival

Pool 2: Supportive studies (LA02/06, LA08, & Borgna-Pignatti *et al*.)
Excluded from Pool 1 due to design (i.e. non-controlled; natural history) or to endpoints other than cardiac

Pool 3: 'Other' studies (LA01, LA03, LA04/06B, LA11, LA15)
Compassionate-use programs, Investigator-driven, Non-GCP compliant

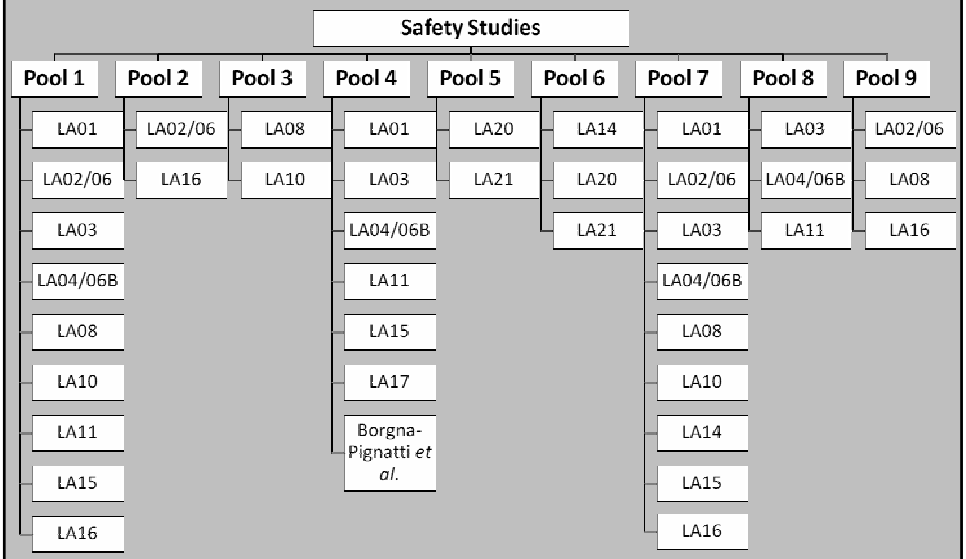
FERRIPROX® (deferiprone, DFP) – NDA 21-825

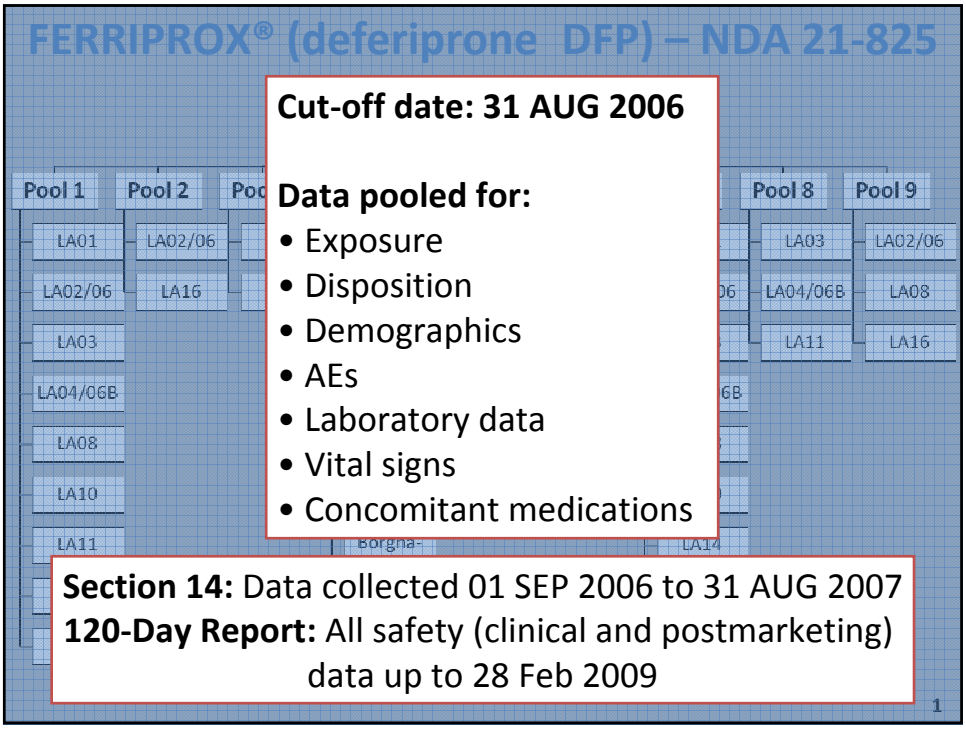
ISS - Data Pools

Pool 1: All clinical studies with safety data
Pool 2: Primary studies
Pool 3: Supportive studies
Pool 4: "Other" studies
Pool 5: Healthy volunteers
Pool 6: Single-dose studies
Pool 7: Subjects with thalassemia major
Pool 8: Subjects with transfusional iron overload conditions other than thalassemia major
Pool 9: Long-term (≥ 1 year) studies

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS – Pool Summary





FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS - Pool 1 - Clinical Studies

	DFP 50 mg/kg/d	DFP 75 mg/kg/d	DFP 100 mg/kg/d	DFP (all doses)	DFO (all doses)	Alternating Doses of DFP and DFO
Subjects Exposed [N]	24	374	29	456	118	29
Subject-Years' Exposure	26	916	27	998	129	28
Length of Exposure (years)						
Mean ± SD	1.08 ± 0.56	2.45 ± 2.33	0.94 ± 0.20	2.19 ± 2.18	1.10 ± 0.74	0.96 ± 0.04
Median	1.23	1.94	0.98	1.18	0.99	0.98
Min, Max	0.0, 1.6	0.0, 11.0	0.1, 1.1	0.0, 11.0	0.1, 2.7	0.9, 1.1

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS - Pool 1 – Baseline Characteristics

	DFP 50 mg/kg/d (n = 24)	DFP 75 mg/kg/d (n = 374)	DFP 100 mg/kg/d (n = 29)	DFP (all doses) (n = 456)	DFO (n = 118)	Alternating DFP and DFO (n = 29)
Primary Disease [n (%)]						
Thalassemia Major	0	343 (91.7)	29 (100.0)	401 (87.9)	118 (100.0)	29 (100.0)
Other*	24 (100.0)	31 (8.3)	0 (0.0)	55 (12.1)	0 (0.0)	0 (0.0)

* Aplastic Anemia, Beta−Thalassemia/Hemoglobin E Disease, Diamond-Blackfan Anemia, Chronic Lymphocytic Leukemia, Congenital Sideroblastic Anemia, Erythropoietin-Resistant Anemia, Myelodysplasia, Myelofibrosis, Pure Red Cell Aplasia, Severe Hemolytic Anemia, Sickle Cell Disease, Thalassemia Intermedia, Transfusion-Dependent Aase Syndrome, Transfusion-Dependent Refractory Anemia

FERRIPROX® (deferiprone, DFP) – NDA 21-825

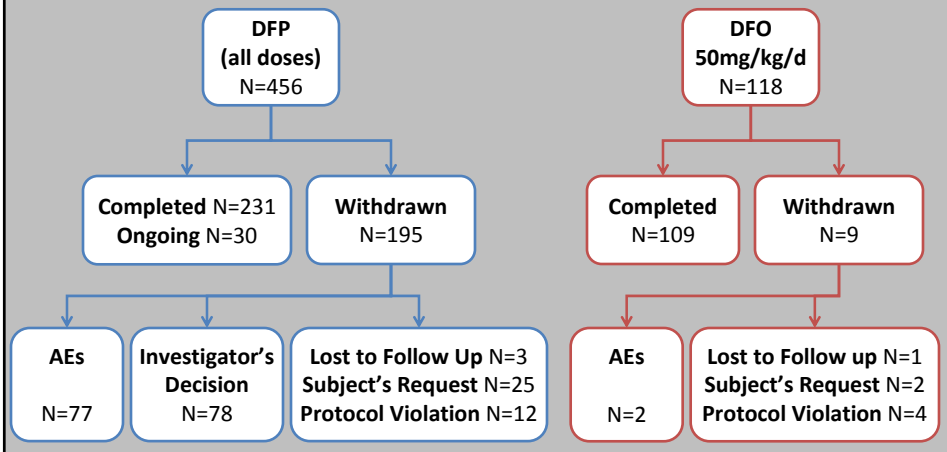
ISS - Pool 1 – Baseline Characteristics

	DFP 50 mg/kg/d (n = 24)	DFP 75 mg/kg/d (n = 374)	DFP 100 mg/kg/d (n = 29)	DFP (all doses) (n = 456)	DFO (n = 118)	Alternating DFP and DFO (n = 29)
Baseline ALT [n (%)]						
≤2 × ULN	20 (83.3)	278 (74.3)	25 (86.2)	350 (76.8)	97 (82.2)	27 (93.1)
>2 × ULN	4 (16.7)	94 (25.1)	4 (13.8)	104 (22.8)	21 (17.8)	2 (6.9)
Missing Data	0	2 (0.5)	0	2 (0.4)	0	0
Baseline ANC [n (%)]						
$<1.5 \times 10^9$/L	0	8 (2.1)	0	8 (1.8)	1 (0.8)	0
$\geq 1.5 \times 10^9$/L	24 (100.0)	363 (97.1)	29 (100.0)	445 (97.6)	117 (99.2)	29 (100.0)
Missing Data	0	3 (0.8)	0	3 (0.7)	0	0

Note: "Missing Data" includes data that was either missing or was not applicable

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Disposition of DFP- and DFO-treated subjects in Pool 1



FERRIPROX® (deferiprone, DFP) – NDA 21-825

Potential Factors for the Difference in Withdrawals

1) Long duration (up to 11 years) of studies with no DFO control group.

   Withdrawals in Pool 1 controlled studies:

   - DFP = 10 (9%); 8 per 100 subject-year exposure
   - DFO = 9 (8%); 7 per 100 subject-year exposure

2) Comparison of a new therapy (DFP) to a therapy that had been used over the long-term (DFO)

3) Lack of chelation alternatives for DFO-treated subjects

4) No dose adjustment for DFP

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Lack of Efficacy Adverse Events

Three terms related to lack of efficacy identified:

1. **Serum ferritin increased**
2. **Hepatic siderosis** (verbatim term Increased Hepatic Iron Concentration (HIC)
3. **Drug ineffective**

When reported as AEs, they were reclassified as "Lack of Efficacy" and were presented separately from AE/ADR calculations

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS – Adverse Events – Pool 1

	DFP Treatment (All Regimens)	DFO treatment
Adverse Events (n)	6365	1153
Treatment Exposure (Subject Years)	998	129
Adverse Events per 100 subject years	**638**	**892**

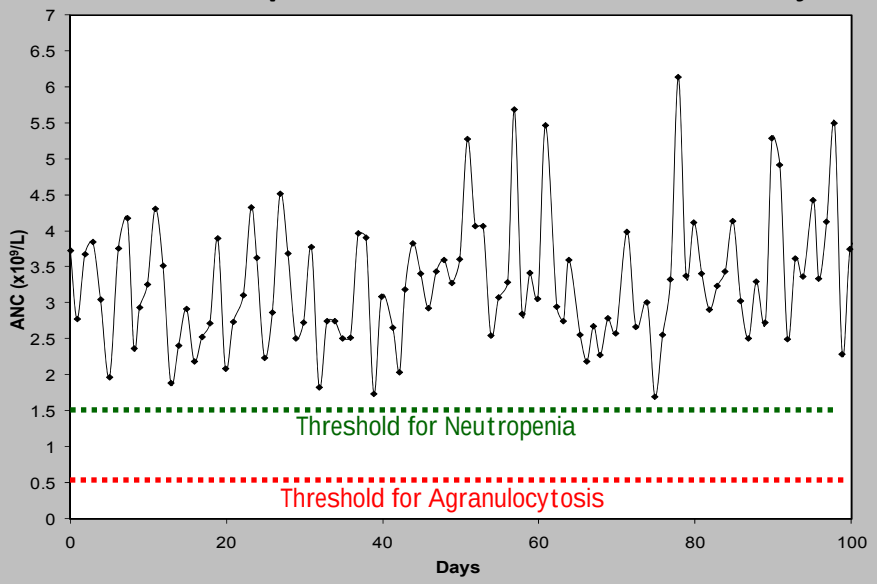
FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS – Neutropenia Pool 1

	DFP (all doses)	DFO (all doses)
Frequency [n(%)]	30/456 (7%)	5/118 (4%)
Rate per 100 Subject Years	3.2	4.6

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ANC in a Non-Splenectomized Thalassemia Subject



FERRIPROX® (deferiprone, DFP) – NDA 21-825

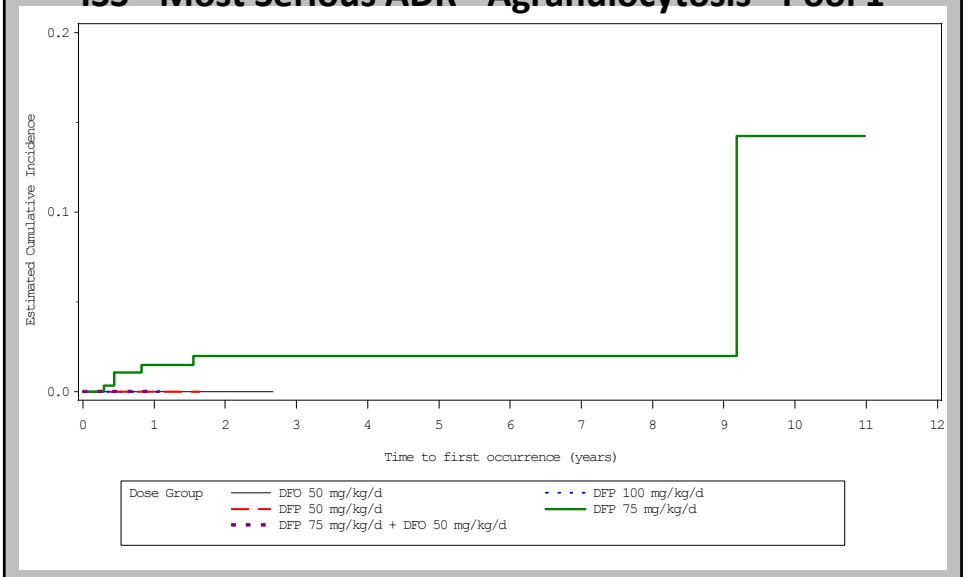
ISS - Most Serious ADR - Agranulocytosis - Pool 1

- Agranulocytosis is the most clinically significant ADR related to DFP

	DFP (all doses)	DFO (all doses)
Frequency [n(%)]	7/456 (2%)	0/118 (0%)
Rate per 100 Subject Years	0.7	0.0

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS - Most Serious ADR - Agranulocytosis - Pool 1



FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS - Listing of Reported Deaths in Clinical Studies

Unique Subject ID	Treatment Group	Time (days)*	Cause of Death (Preferred Term)	Relationship to Study Medication**
LA-01-61	DFP (75 mg/kg/d)	170 [30]	Cardiac failure congestive	Doubtful
LA-0206-604	DFP (75 mg/kg/d)	1706 [20]	Internal injury	Not related
LA-04-38	DFP (75 mg/kg/d)	46 [7]	Cardiac failure	Doubtful
LA-04-39	DFP (75 mg/kg/d)	180 [29]	Multiorgan failure	Not related
LA-04-49	DFP (75 mg/kg/d)	2681 [23]	Postprocedural complication†	Not related
LA-04-109	DFP (75 mg/kg/d)	157	Cardiomyopathy‡	Not related
LA-04-114	DFP (75 mg/kg/d)	242	Cardiac failure	Not related
LA-04-127	DFP (75 mg/kg/d)	302 [108]	Lung neoplasm malignant	Not related
LA-04-172	DFP (75 mg/kg/d)	26 [1]	Cardiac failure	Not related
LA-11-107	DFP (50 mg/kg/d)	146 [2]	Diarrhoea	Doubtful

*Time is the number of days that the subject had stayed on the study treatment at the time of the death. If the death occurred after discontinuation, the number of day on study treatment is displayed, followed by the number of days from the time of discontinuation to the time of death in square brackets.
†The "post procedural complication" preferred term is linked to the primary SAE "fracture" for the same subject
‡The "cardiomyopathy" preferred term is linked to the SAE "sepsis" for the same subject.
** Relationship to Study Medication based on investigator's reported assessment of causality.

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISS - Post Marketing Experience

- Data obtained between 25 AUG 1999 to 31 AUG 2006 are presented in the NDA Clinical and Statistic Reviewable Unit
  - 14,875 patient-years postmarketing exposure
  - No new serious health concerns have been identified
  - Changes to SPC include addition of headache, fatigue, diarrhea, and risk of reversible neurological disorder associated with chronic overdose (>200 mg/kg/day > 1 year)

(b) (4)

NDA 21-825
FERRIPROX® (deferiprone, DFP)

Integrated Summary of Efficacy

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Data Pools

Pool 1: Pivotal studies (LA12 & LA16)

Studies where efficacy endpoints support the proposed indication:

- Cardiac iron concentration
- Cardiac function
- Cardiac morbidity
- Survival

T2* Evaluation of Myocardial Iron

Dudley Pennell MD FRCP FACC FESC

Professor of Cardiology
Director Cardiovascular MR Unit
Director Non-invasive Cardiology
Director NIH Research BRU on Cardiac Regeneration

(b) (4)

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Pool 1: Study LA12

- **Post-marketing commitment to EMEA**
- **Prospectively designed**
- **Study design & protocol approved by the EMEA prior to any data collection**
- **Compared cardiac disease and mortality in transfusion dependent subjects with β -thalassemia who had received long-term treatment with DFP or DFO (retrospective and prospective data)**

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - New York Heart Association (NYHA) Classification

The four-tier NYHA classification of functional capacity is commonly used to estimate prognosis in clinical practice and to define study populations in clinical trials

- **Class I (Mild)**: No limitation of physical activity
- **Class II (Mild)**: Slight limitation of physical activity
- **Class III (Moderate)**: Marked limitation of physical activity
- **Class IV (Severe)**: Unable to carry out any physical activity without discomfort; Death

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - New York Heart Association (NYHA) Classification

The fo… …y is com… …actice and…

- **Clas…**
- **Clas…**
- **Clas…** acti…
- **Clas…** activity without discomfort; Death

- **Worsening** of the NYHA classification was defined as increasing in NYHA class over the exposure to study drug
- **Improvement** of NYHA was defined as decreasing in NYHA class over the exposure to study drug
- **Development of cardiac disease** was defined as first occurrence of NYHA class of I or greater during the exposure to study drug

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Pool 1 - Cardiac Disease and Survival (LA12)

Piga *et al*., 2003

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Pool 1 - Cardiac Disease and Survival (LA12)

COPYRIGHT MATERIAL

Piga *et al*., 2003

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Pool 2 - Supportive Studies

Pool 2: Supportive studies (LA02/06, LA08, Borgna-Pignatti *et al*.)

The supportive studies used to evaluate the efficacy of DFP are studies that were excluded from the "pivotal" category because of study design (i.e. single arm design, no cardiac endpoints, natural history)

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Borgna-Pignatti *et al*. - Natural History Studies on Survival of Thalassemia Major Patients

- Multicentre study initiated in 1983 by 7 of the major Thalassemia Centres in Italy
- Follow up of all patients treated from diagnosis in those centres
- Results published
  - 1989 - The Lancet
  - 1993 - Bone Marrow Transplant
  - 1998 - Ann N Y Acad Sci.
  - 2004 - Haematologica
  - 2005 - Ann N Y Acad Sci.
  - 2006 - Blood

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Borgna-Pignatti *et al*. - Study Design

- Natural history study
- Patients born between 1970-1993 and who were alive and had **not** had a cardiac event prior to 31 Jan 1995
- Last follow-up 31 Dec 03
- Efficacy end point: Clinical Outcome
- SAP prospectively designed

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Borgna-Pignatti *et al*. - Incidence of Cardiac Event

Year*	Deferoxamine			Deferiprone		
	Subjects at Risk	Cardiac Events	Percentage (95%CI)	Subjects at Risk	Cardiac Events	Percentage (95%CI)**
1995	516	**3**	0.58 (0.12, 1.69)	0	**0**	-
1996	444	**11**	2.48 (1.24, 4.39)	63	**0**	0 (0, 5.69)
1997	420	**4**	0.95 (0.26, 2.42)	75	**0**	0 (0, 4.80)
1998	398	**5**	1.26 (0.41, 2.91)	93	**0**	0 (0, 3.85)
1999	396	**3**	0.76 (0.16, 2.20)	89	**0**	0 (0, 4.06)
2000	393	**4**	1.02 (0.28, 2.59)	87	**0**	0 (0, 4.15)
2001	387	**6**	1.55 (0.57, 3.34)	89	**0**	0 (0, 4.06)
2002	374	**4**	1.07 (0.29, 2.72)	88	**0**	0 (0, 4.30)
2003	358	**12**	3.35 (1.74, 5.78)	92	**0**	0 (0, 3.93)

*Each subjects is included once in each year, based on the treatment received on January 1 of that year.

**One-sided 97.5% confidence interval.

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Borgna-Pignatti *et al*. - Hazard Ratio

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Borgna-Pignatti *et al*. - Distribution of Death

	DFO-only (n = 359)	DFP-switched (n = 157)
Death due to cardiac cause	15	0

FERRIPROX® (deferiprone, DFP) – NDA 21-825

ISE - Borgna-Pignatti *et al*. - Conclusions

- Patients who switched to deferiprone therapy had a remarkably lower prevalence of cardiac disease and cardiac death in spite of a heavier starting iron overload
- No cardiac events occurred during deferiprone therapy or within at least 18 months after the end of it
- Deferiprone was associated with significantly greater cardiac protection than deferoxamine in patients with thalassemia major

Disorders of Erythropoiesis

Risk factors for death in patients with β-thalassemia major: results of a case-control study

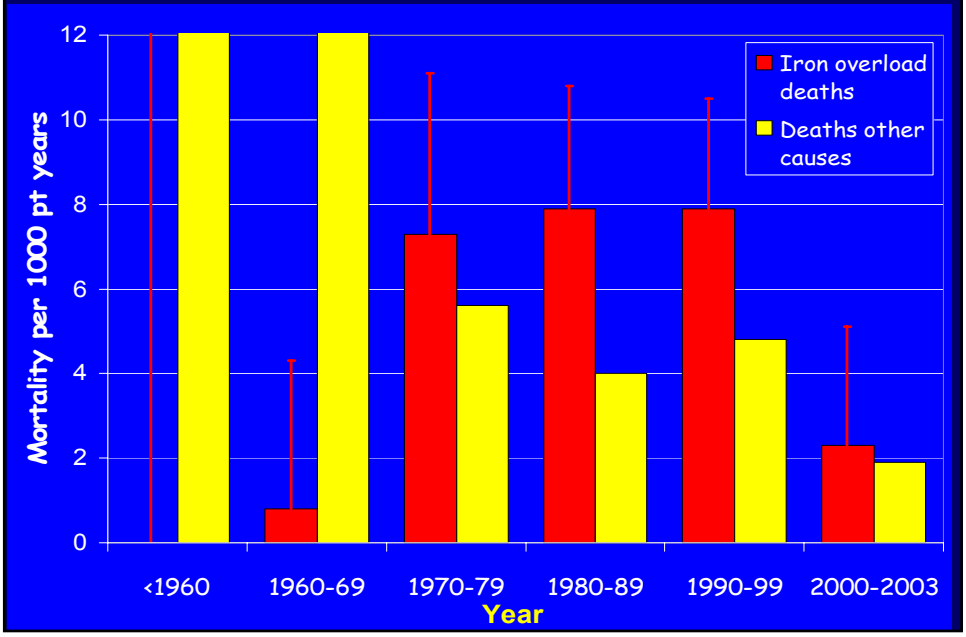
COPYRIGHT MATERIAL

Disorders of Erythropoiesis • Research Paper

Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980-2004

Haematologica 2006; 91:1187-1192

Mortality rates over 5 yr time periods



FERRIPROX® (deferiprone, DFP) – NDA 21-825

Maggio *et al*. - Blood Cells, Molecules, and Diseases - 2009

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Maggio *et al*. - Blood Cells, Molecules, and Diseases - 2009

FERRIPROX® (deferiprone, DFP) – NDA 21-825

Upcoming Actions

- **Response to the Filing Communication letter**
  - Will be submitted by 06 May 2009
- **Day 120 Safety Update Report (cut off: 28 Feb 2009)**
  - Includes LA30 clinical study report
  - Re-integrate Pool 1 safety data from 1993 to 28 Feb 2009 and present any differences from data presented in the ISS
- **Rat Fertility and Early Embryonic Development Study**
  - In-life phase completed
  - Final Draft Report expected June 2009
- **Proprietary Name Review Request**
- **Minor amendments to the CMC module**

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

/s/

Hyon Z Lee
4/20/2009 05:48:39 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-825

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA)-Pilot 1 program, for deferiprone 500 mg film-coated tablet.

We also refer to your submissions dated December 21, 2006, September 26 (2) and December 21, 2007, March 19 and 27, June 27, September 15 and 29, October 30, 2008 and February 17, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 30, 2009.

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 October 15, 2009.

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

Clinical:

1. The indication being proposed is for the treatment of iron overload in patients with transfusion-dependent thalassemia; and for the treatment of iron overload associated with other transfusion-dependent anemias for whom the treatment of other iron chelators has been considered inappropriate. Studies LA16-0102 and LA12-9907 enrolled only subjects with thalassemia. Virtually all the other data provided also related to patients with thalassemia. The indication, if approved, will apply to the population in which efficacy and safety have been demonstrated.

2. In Study LA16-0102, one of the exclusion criteria was "subjects who have disorders associated with neutropenia or thrombocytopenia". This exclusion criterion may importantly impact the interpretation of the study data and the development of product labeling. Additional studies may be necessary to address these limitations.

3. The proposed initial dosage of deferiprone for the indication (75 mg/kg/day) is different from the dosage that was used in Study LA16-0102 (start at 75 mg/kg/day, increase to 85 mg/kg/day at week 4, then increase to 100 mg/kg/day at week 8).

4. A robust quantitative relationship between MRI T2* and change in cardiac iron concentration in humans has not been established.

5. Clinical meaningfulness has not been established for change in MRI T2* as an expression of change in cardiac iron concentration in humans.

6. You have not provided data that show that an increase in cardiac MRI T2*, LVEF or LVSF translates to any clinically meaningful improvement in morbidity or mortality in patients with thalassemia.

7. You have provided analyses of data that you state indicate statistical differences between treatment with deferiprone and deferoxamine, but you appear not to have demonstrated that these small differences permit inferences about the clinical utility of deferiprone.

8. You appear to have misquoted reference number 9 on page 117, and reference numbers 59 and 62 on pages 121-122 of the study report of Study LA16-0102 in regard to the applicability of cardiac MRI T2* assessments.

9. You have not provided clear and complete explanations for the early termination of some of your studies.

10. You state that Study LA16-0102 was a multi-institutional trial. However, 56 of the 61 subjects enrolled came from only two institutions.

11. It appears that the appointment of the MRI reader (Dr. Pennell) post-dated the enrollment of subjects in the trial.

12. The statistical analysis plan for Study LA16-0102 appears to post-date the completion of the trial. Statistical analysis plans should preferably be pre-specified in the protocol.

13. The references provided to support the clinical significance of changes in the LVEF and the LVSF were based entirely on echocardiography (rather than MRI) and virtually all the patients evaluated had coronary artery disease as the cause for congestive heart failure (CHF). In addition, most of the patients had a subnormal LVEF or LVSF. Therefore, these data may not be applicable to CHF due to hemosiderosis of the heart.

14. The demographic characteristics of the patients were dissimilar in the 2 arms of the LA16-0102 trial, raising questions about the success of the randomization process. Patients assigned to the deferoxamine arm were older, were more likely to have been splenectomized and had higher baseline levels of serum ferritin. This suggests that the subjects assigned to deferoxamine had more severe thalassemia than those assigned to deferiprone.

Labeling (Physician's Labeling Rule Format):

1. Highlights:

   - The "**Initial U.S. Approval**" statement must be followed by the four-digit year and be placed on the line immediately beneath the name of the product.
   - The verbatim statement "**See full prescribing information for complete boxed warning**" must be placed immediately following the heading of the boxed warning.
   - In the Adverse Reactions section, the verbatim statement, "**To report SUSPECTED ADVERSE REACTIONS, contact ApoPharma, Inc. at (manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**" must be bolded.

2. Full Prescribing Information (FPI): Contents:

   - The heading, "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be bolded.
   - The same title for the boxed warning that appears in the Highlights and FPI must also appear at the beginning of the Table of Contents in upper-case letters and bold type (i.e., **WARNING: NEUTROPENIA/AGRANULOCYTOSIS**).
   - Table of Contents section headings must be in bold type and should be in upper-case letters. There are no periods after the numbers for the section and subsection headings.

3. Full Prescribing Information (FPI):

   - The Boxed Warning section must include brief concise summary of critical information, with a cross-reference to more detailed discussion in other sections.

- Do not use all capital letters to cross-reference. For example, [see *Indications and Usage (X,X)*].
- The adverse reactions profile in Table 2 should be in lower case letters.

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:

Statistical:

Refer to clinical comment 1; apparently no efficacy and safety data are provided that support an indication for your product in the treatment of iron overload associated with other transfusion-dependent anemias for whom the treatment of other iron chelators has been considered inappropriate. Please provide efficacy and safety data in appropriate format that directly relate to the indications being sought. You may also revise the indication to the population in which efficacy and safety have been demonstrated.

Chemistry, Manufacturing and Controls (CMC):

1. Provide the procedures used to qualify a drug substance lot for reduced testing or re-testing at the drug substance and drug product manufacturing sites. Include a justification for the proposed procedures.

2. Regarding the response to comment 3 of the Discipline Review letter dated March 27, 2008, the submitted certificates of technology transfer are not an acceptable surrogate for the requested method validation study reports. Provide a copy of the method validation reports for the studies performed at each of the drug substance manufacturing sites. The studies should be complete and the reports include copies of the appropriate chromatograms.

3. Either verify that the method validation studies for the revised drug product specification methods were performed at the Apotex-Etobicoke site or provide a copy of the method validation reports from that site. The study should be complete and the reports should include copies of the appropriate chromatograms.

4. Revise the master production record to include an acceptance criteria for percent yield as mandated under 21 CFR 211.186(b)(7).

If you have not already done so, you must 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. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information within 30 days of receipt of this letter. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

However, because your drug has an orphan drug designation, you are exempt from this requirement.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Rafel Rieves

3/31/2009 02:08:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825

PROPRIETARY NAME REQUEST
- UNACCEPTABLE

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA)-Pilot 1 program, for deferiprone 500 mg film-coated tablet.

We also refer to your February 25, 2009, correspondence, received February 25, 2009, requesting review of your proposed proprietary name, Ferriprox. We have completed our review and have concluded that this name is unacceptable for the following reasons:

The Division of Medication Error and Prevention Analysis (DMEPA) believes that the name, "Ferriprox", may be misleading to practitioners and patients by leading them to assume that Ferriprox is an iron "supplement" drug product. DMEPA is concerned that the beginning letters of Ferriprox ("Ferr") may infer that this product contains iron and is to be used for iron replacement instead of iron overload. Although "fer-" and "ferr-" are not USAN stems, there are multiple prescription and non-prescription iron-containing products on the market that begin with these letters, for example, Ferrlecit, Fergon, Feratab, and Fer-In-Sol, to name a few. All of the aforementioned products are iron supplements. Additionally, DMEPA conducted a search of the Orange Book for products that contain the prefix "fer" or "ferr" and are not used for iron supplementation. We found one product, Feridex I.V. (ferumoxides) that is currently available that met those criteria. Feridex I.V. is classified as a radiological/contrast media product. The other products identified in the search have been discontinued: Fernisone (prednisone), Fernisolone-P (prednisolone), Ferrous Citrate Fe-59, Ferriseltz (ferric ammonium citrate), Ferndex (dextroamphetamine), and Fertinex (urofollitropin). Additionally, we identified two currently available iron chelators, Desferal (deferoxamine mesylate) and Exjade (deferasirox). Neither of these proprietary names contains the beginning "Fer" or "Ferr" letters. Because the name Ferriprox strongly suggests that the product is an iron supplement when in fact it is indicated as a treatment for iron overload, DMEPA believes that confusion can ensue regarding the product's suggested versus its actual indication. Therefore, DMEPA does not recommend

the use of the proposed proprietary name, Ferriprox, because it may mislead practitioners into believing that it is an iron supplement drug product rather than a drug which is used to treat iron overload.

In the review of the container label and insert labeling of Ferriprox, DMEPA has focused on safety issues relating to possible medication errors. DMEPA has identified the following areas of improvement to minimize potential user error.

A. CONTAINER LABEL (500 mg tablets)

1. Please ensure that the established name is at least one-half the size of the proprietary name, in accordance with 21 CFR 201.10(g)(2). Add the dosage form, "tablets", to the established name. Delete the words "Film-coated" as part of the established name and finished dosage form. This statement is a descriptor and can appear below the strength (see the example in recommendation number 2, below).

2. Reposition the statement of strength so that it appears below the finished dosage form (see example below) and increase its size to provide more prominence.

   Example:
   Ferriprox
   Deferiprone Tablets
   500 mg
   (Film-coated Tablets)

3. [redacted] (b) (4)

4. Insert the wording "Usual Dosage" prior to the statement [redacted] (b) (4). Consider revising the [redacted] (b) (4) statement to: "See the package leaflet for full prescribing information" or similar verbiage.

5. Currently, the sponsor's trade logo and manufacturer information are more prominent than other important information such as the proprietary name, established name, and strength. Decrease the size of the manufacturers name or remove the [redacted] (b) (4) in order to decrease its prominence.

B. INSERT LABELING

In the DOSAGE AND ADMINISTRATION section of the package insert labeling, one of the sentences states: [redacted] (b) (4) (see the sample below, taken from the package insert labeling). Please clarify the sentence to read: [redacted] (b) (4) so that "mg/kg" is placed next to each numerical dose specification. This may help to minimize any potential for confusion about the dose.

2 DOSAGE AND ADMINISTRATION

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions, call Hyon-Zu Lee, Regulatory Health Project Manager, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Rafel Rieves

3/24/2009 12:49:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA)-Pilot 1 program, for deferiprone 500 mg film-coated tablet.

We also refer to your submission dated March 10, 2009.

We have reviewed your proposal for the content and format of the 120 day safety update report and find it acceptable. Please note that we will request additional information if other specific analyses or presentations of particular safety data are needed during review of the application.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Rafel Rieves

3/16/2009 02:58:07 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for deferiprone 500 mg film-coated tablet.

This is an application orientation meeting for you to present your development status of deferiprone. Please provide an electronic copy of the slides 24 hours prior to the meeting. A proxima will be available. Structure your presentation for approximately 45 minutes, leaving 45 minutes for questions and discussion. Your presentation should summarize the data that you are relying on to support market approval.

Based on the statement of purpose, objectives, and 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: April 13, 2009
Time: 2 PM – 3:30 PM (Eastern Standard Time)
Location: FDA/CDER
10903 New Hamsphire Ave., Building #22, Room # 1415
Silver Spring, MD 20993

CDER participants: Richard Pazdur, M.D., Office Director
Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
George Shashaty, M.D., Medical Reviewer
Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology Team Leader
Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer
William Adams, Ph.D., Chemistry Reviewer
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Paul Hepp, Pharm.D., Clinical Pharmacology Reviewer
Aloka Chravarty, Ph.D., Director, Division of Biostatistics V
Satish Misra, Ph.D., Statistics Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

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 Hyon.Lee@fda.hhs.gov so that I can give the security staff 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: Hyon-Zu Lee, at 301-796-2192; the division secretary, at 301-796-2050.

If you have any questions, call me, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Hyon Z Lee

2/25/2009 04:45:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825

NDA ACKNOWLEDGMENT

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

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

Name of Drug Product: Ferriprox® (deferiprone) 500 mg Film-Coated Tablet

Date of Application: January 29, 2009

Date of Receipt: January 30, 2009

Our Reference Number: NDA 21-825

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 March 31, 2009 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

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 Medical Imaging and Hematology 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 question, call me, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Hyon Z Lee

2/5/2009 03:44:51 PM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE
Attn: Janet Anderson, Mary Dempsey

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Medical Imaging and Hematology Products (HFD-160)
Hyon-Zu Lee, (301) 796-1292

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 26, 2009		21-825	New NDA	January 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
deferiprone tablets	Standard	Metal Chelator	September 30, 2009

NAME OF FIRM: ApoPharma, 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:

The purpose of this consult is to request review of the Risk Management for a new NDA 21-825, deferiprone tablet.

The HFD-160 Medical Officer is George Shashaty (301-796-1458), and the Regulatory Project Manager is Hyon-Zu Lee (301-796-2192).

Please note that the NDA is in the EDR.

The proposed review due date of September 30, 2009 is negotiable pending the overall review of this NDA.
Thank you for your assistance, and feel free to call me if you have any questions.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

Hyon-Zu Lee	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Hyon Z Lee

2/26/2009 11:42:22 AM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health Staff
Attn: Tammie Brent-Steele

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Medical Imaging and Hematology Products (HFD-160)
Hyon-Zu Lee, (301) 796-1292

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 26, 2009		21-825	New NDA	January 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
deferiprone tablets	Standard	Metal Chelator	September 16, 2009

NAME OF FIRM: ApoPharma, 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:

This is a new NDA submitted on January 29, 2009.

Please review the proposed labeling regarding Pediatric and Maternal Health for this application. Please note that the NDA is in the EDR. The labeling can be found in Module 1.

The HFD-160 Medical Officer is George Shashaty (301-796-1458), and the Regulatory Project Manager is Hyon-Zu Lee (301-796-2192).

We would like your consult review to be finalized in DFS by September 16, 2009.
Thank you for your assistance, and feel free to call me if you have any questions.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

Hyon-Zu Lee	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Hyon Z Lee

2/26/2009 11:05:06 AM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DMIHP, Libero Marzella, M.D., Ph.D.	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Medical Imaging and Hematology Products (HFD-160) Hyon-Zu Lee, Pharm.D. (301) 796-1292

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 26, 2009		21-825	New NDA	January 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
deferiprone tablets	Standard	Metal Chelator	September 16, 2009

NAME OF FIRM: ApoPharma, 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:

We have a new NDA 21-825 submitted on January 29, 2009 for deferiprone tablets.

The purpose of this consult is to address the current status of cardiac MRI T2* assessment as a measure of cardiac iron content and the clinical significance of a small change in MRI T2* after treatment with deferiprone and deferoxamine

The HFD-160 Medical Officer is George Shashaty (301-796-1458), and the Regulatory Project Manager is Hyon-Zu Lee (301-796-2192).

This is an eCTD submission.

We would like your consult review to be finalized in DFS by September 16, 2009.
Thank you for your assistance, and feel free to call me if you have any questions.

SIGNATURE OF REQUESTOR Hyon-Zu Lee	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Hyon Z Lee

2/26/2009 10:53:12 AM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
DDMAC, Michelle Safarik

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Medical Imaging and Hematology Products (HFD-160)
Hyon-Zu Lee, (301) 796-1292

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 26, 2009		21-825	New NDA	January 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
deferiprone tablets	Standard	Metal Chelator	September 16, 2009

NAME OF FIRM: ApoPharma, 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:

The purpose of this consult is to request review of the proposed labeling for a new NDA 21-825 submitted on January 29, 2009 for deferiprone.

The HFD-160 Medical Officer is Goerge Shashaty (301-796-1458), and the Regulatory Project Manager is Hyon-Zu Lee (301-796-2192).

This is an eCTD submission. The labeling information can be found in Module 1.

We would like your consult review to be finalized in DFS by September 16, 2009.
Thank you for your assistance, and feel free to call me if you have any questions.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

Hyon-Zu Lee	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Hyon Z Lee

2/26/2009 09:56:14 AM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, December 16, 2008 11:16 AM
To: 'Lynda Sutton'
Subject: NDA 21-825: FDA response to the Nov. 26, 2008 submission

Ms. Sutton,

We have reviewed your November 26, 2008 submission containing Amendment to the Pharmacology and Toxicology Reviewable Unit.

Your proposed outline of the protocol for the male and female fertility study and the timetable for submission of the final report are acceptable.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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

/s/

Hyon Z Lee
12/16/2008 11:21:52 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/Reviewable Unit-PT

INFORMATION REQUEST LETTER

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) for Ferriprox®(deferiprone) 500 mg Film-Coated Tablet submitted under the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to your submission dated September 15, 2008, amendment to the Pharmacology and Toxicology Reviewable Unit, the Agency's letter dated August 7, 2008, and have the following comment.

We re-iterate that you should provide the final study report for the fertility and early embryonic development study for review prior to or with the Clinical Reviewable Unit submission. Post approval submission of this report is not acceptable.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Rafel Rieves

9/24/2008 11:04:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/Reviewable Unit-PT

INFORMATION REQUEST LETTER

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) for Ferriprox®(deferiprone) 500 mg Film-Coated Tablet submitted under the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to your submission dated March 19, 2008, amendment to the Pharmacology and Toxicology Reviewable Unit and have the following comment and information requests.

1. The two carcinogenicity study protocols for special protocol assessment (SPA) review must be provided separately and not in the same submission.

2. Please provide final study reports for the electrophysiology study and the fertility and early embryonic development study for review prior or with the Clinical Reviewable Unit submission.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Kyong Kang
8/7/2008 02:51:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-825/Reviewable Unit-Clinical Pharmacology

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) for Ferriprox®(deferiprone) 500 mg Film-Coated Tablet, submitted under the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to your September 26, 2007 reviewable unit (RU) for the Clinical Pharmacology portion of your NDA.

We have completed our review of this RU and have identified the following deficiencies:

We request a prompt written response in three months.

1. The study results submitted from thalassemic subjects with cirrhosis is not useful for purposes of assessing the effects of varying degrees of hepatic dysfunction related to the disposition of deferiprone. A hepatic function classification system such as the Child-Pugh that would differentiate degrees of hepatic dysfunction was not utilized in study LA14-9907 (cirrhotic study). Since the deferiprone is extensively metabolized after oral administration (about 95% to the glucuronide), it is important that disposition be investigated in subjects with varying degrees of hepatic dysfunction.

2. You did not submit a study related to the effect of renal dysfunction on the pharmacokinetics of deferiprone or the major glucuronide metabolite. Since the glucuronide metabolite which represents about 95% of an orally ingested dose of deferiprone is excreted renally, it is important that disposition be investigated in subjects with varying degrees of renal dysfunction.

3. PK study of deferiprone chronically administered at the upper approved dosage level (33 mg/kg tid) has not been studied, and the degree of accumulation (expected vs. observed) under those conditions is unknown. Study to evaluate the PK of deferiprone at the upper labeled dosage level of 33 mg/kg tid under chronic dosage conditions should be conducted.

4. Dose proportionality: Single dose PK studies at the labeled dose of 25-33 mg/kg have not been conducted (only a 21 mg/kg single dose study was conducted). Study to evaluate dose proportionality between the 25 and 33 mg/kg dosage levels should be conducted.

5. You have not submitted any drug interaction study results for deferiprone in this application. Drug interaction Information should be provided (see FDA Guidance on drug interactions related to this).

6. The analytical standard curve and QC information as well as the individual biologic sample results related to the assays as used in all three studies (LA20-BA, LA01-PK, LA14-9907) have not been included in the September 26, 2007 submission. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

7. The individual subject PK results for studies (LA20-BA, LA01-PK, LA14-9907) were not submitted in the September 26, 2007 application. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

8. GC-Mass Spec analytical methods were developed by (b) (4) to determine the bioavailability of the Ferriprox® tablets for study LA20-BA (An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions). Method AA20080-VTL was developed for quantitating deferiprone and deferiprone glucuronide in serum samples. Method AA20743-WCM was developed for quantitating deferiprone and deferiprone glucuronide in urine. During the review of the subject submission, it was determined that analytical evaluation for study LA20-PK was performed by (b) (4) during a period including December, 2004. This time relates to a period when FDA inspections of two (b) (4) facilities raised questions about the validity and accuracy of test results from studies conducted by (b) (4). FDA has previously decided that for studies falling under this situation, that the one of the following would be necessary :

    - perform an independent audit of the results
    - re-assay the samples (if retained and stable)
    - repeat the study

    Study LA20-PK is a required study for approval of the product (required bioavailability study), so its acceptability does need to be established. At this point, an independent audit of the (b) (4) assays as used in study LA20-PK (standard curves, quality control samples, etc) and an audit of the individual study sample results should be arranged by the sponsor. Depending on the results of the independent audits, the need for any other steps will be determined by the Agency.

9. You have not conducted studies to assess the potential of QT prolongation of deferiprone.

10. ApoPharma has not conducted any studies to address the effect of age on the pharmacokinetics of Ferriprox®. Literature citations made related to the effect of age on the pharmacokinetics of deferiprone are inadequate to make any age related conclusions or labeling statements. The draft labeling should and does reflect this situation. You should investigate age effects related to deferiprone, and provide resultant information for labeling purposes.

11. You have not addressed how you chose its selected dosing from a dose response standpoint. Information to support this should be presented.

We are providing these comments to you before we complete our review of the complete application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Kyong "Kaye" Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Kyong Kang
3/27/2008 03:51:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-825/ Reviewable Unit-CMC

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) for Ferriprox®(deferiprone) 500 mg Film-Coated Tablet, submitted under the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to the Chemistry, Manufacturing, and Controls (CMC) reviewable unit portion of your NDA submitted on March 12, 2007 and September 26, 2007, and the amendment submitted on December 21, 2007. We acknowledge that the March 12, 2007 submission was withdrawn on July 26, 2007.

As stated in our information request letter dated February 28, 2008, the September 26, 2007 and December 21, 2007 submissions do not include the complete CMC reviewable unit, therefore the March 12, 2007 submission has been included in the review in order to provide preliminary review findings.

We have completed our review of this RU and have identified the following deficiencies:

We request a prompt written response in three months.

Please note that for a complete CMC reviewable unit, information addressing drug substance from all three drug substance manufacturing sites and for the drug product must be submitted.

DRUG SUBSTANCE

1. Specify where stability studies on bulk drug substance from each of the three possible manufacturing sites will be performed.

2. For the Related Substances method (RM3078-04), revise the concentration of the reference standard solutions to represent the limits for known (b) (4) and unknown (b) (4) compounds and specify the reporting threshold.

3. Regarding the submitted method validation information:

   (a) Each of the analytical methods should be validated at the primary manufacturing site and should be verified at the other two drug substance manufacturing sites and at the drug product manufacturing site for selectivity, accuracy, precision, linearity, specificity, ruggedness and robustness as described in USP <1225>. Please provide the appropriate studies.

   (b) Since particle size (b) (4) methods are proposed, comparison data on multiple drug substance lots from each of the drug substance manufacturing sites should be provided.

   (c) For the Apotex validation studies for method RM-E078-4 (Related Substances) dated December 4, 1993 and August 20, 1996 (submitted in the N-001 amendment), specify where these studies were performed. In addition, specify whether either study was performed (b) (4). A complete validation study for the (b) (4) HPLC method should be provided. The ranges for this study should support the currently proposed limit for specified impurities (b) (4) and unknown impurities (b) (4). The system suitability criteria should address accuracy of retention times. Copies of representative chromatograms from the linearity, selectivity, and quantitation limit and detection limit studies should be provided.

   (d) For the Torpharm validation report dated August 9, 1994 for testing procedure RM3078-04, revision 1, the example chromatograms show an unstable baseline which requires an artificial baseline order to make peak area measurement and the L1 peak merges with another peak in some chromatograms. Explain how the method is acceptable with such poor quality chromatograms.

   (e) The results of the validation studies for method RM-3078-5 for Assay show that the retention time for drug substance varies significantly, therefore the system suitability criteria should be revised to address accuracy of this parameter.

4. We have evaluated the submitted batch analysis data in NDA section S.4.4 and reached the following conclusions:

   (a) Melting Range results should be reported as the observed temperature range.

   (b) The water content data does not support the proposed criterion. Based on the data for 45 lots, the value for mean plus 3 standard deviations is (b) (4) and all lots were less than this value. Therefore we recommend that the criterion be revised (b) (4)

   (c) The total impurities data does not support the proposed criterion. Based on the data for 45 lots, the value for mean plus 3 standard deviations is (b) (4) and all lots were less than this value. Therefore, we recommend that the criterion be revised (b) (4)

(d) The residual solvents data does not support the proposed criterion. Based on the data for 22 lots reporting actual test data, the value for mean plus 3 standard deviations is (b) (4) ppm and all lots were less than this value. Therefore, we recommend that the criterion be revised from (b) (4) ppm to (b) (4) ppm, and that the test results be reported as "ppm" values.

In addition, the validation studies for these methods should be revised to address the revised criteria.

5. Clarify whether the annual lot of bulk substance placed on stability will be taken from each site manufacturing bulk drug substance that year and not from only one of the three possible sites.

DRUG PRODUCT

6. Provide drug release profiles over 60 minutes using the proposed apparatus, medium and stirring speed for 500 mg tablets from the lots used in the Phase 3 clinical and primary stability studies.

7. Reduced testing is not addressed in NDA section P.4.1, however the COAs in NDA section 4.4 indicate multiple levels of full and reduced testing. Either verify that each lot of each excipient is tested to meet each of the acceptance specifications or describe the protocol for reduced testing.

8. For the dissolution validation study, the accuracy study should be revised to address a range above and below the reference standard solution concentration (b) (4), and the study submitted.

9. The proposed limit for Total Impurities is not supported by the data since the largest reported value is (b) (4) and no formation of degradation products is reported in the room temperature stability studies. We recommend that the criterion be revised (b) (4). In addition, the validation study for the Related Substances method should be revised as necessary to address the revised criterion.

10. Clarify whether reduced testing for acceptance is performed on the packaging components. If yes, then identify the tests routinely performed on packaging component lots.

11. The submitted stability studies do not support the proposed label storage statement and proposed expiry period. Either provide additional studies with storage at ICH intermediate condition (b) (4) and studies to address the low temperature stability of the tablets to support the proposed (b) (4) expiry period at (b) (4) or revise the label storage statement to use the USP room temperature statement.

In addition, we have not yet received a response to our deficiency letter to DMF 10,867. These deficiencies must be resolved for a complete CMC review.

We are providing these comments to you before we complete our review of the complete application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Richard Lostritto
3/27/2008 10:33:02 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/Reviewable Unit-CMC

INFORMATION REQUEST LETTER

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox®(deferiprone) 500 mg Film-coated Tablet.

We also refer to the Chemistry, Manufacturing, and Controls (CMC) reviewable unit submitted on March 12, 2007 and September 26, 2007, and the amendment submitted on December 21, 2007. We acknowledge that the March 12, 2007 submission was withdrawn on July 26, 2007. The September 26 and December 21, 2007 submissions do not include the complete CMC reviewable unit. Therefore, we have included the March 12, 2207 submission in our review in order to provide preliminary review findings. We presume that future amendments will include the missing sections of the CMC reviewable unit.

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

DRUG SUBSTANCE

1. Regarding the proposed manufacturing sites:

   (a) Identify the primary and secondary manufacturing sites.
   (b) Specify whether any contract labs will perform testing of raw materials, intermediates, in-process materials or finished drug substance.

2. Regarding the drug characterization information:

   (a) Specify whether this drug has high or low permeability and identify its BSC class.
   (b) For the UV spectrum in section S.3.1, identify the solvent and the solution concentration.
   (c) For the particle size data in section S.1.3, identify the manufacturing date and manufacturing site for each lot. Provide particle size data on lots from each of the proposed manufacturing sites.

3. Regarding the release specification information on the drug substance:

   (a) Provide the specification (tests, methods and criteria) for release from each manufacturing site and for acceptance at the drug product manufacturing site if the lots are to be re-tested there.
   (b) If the specification is the same for each site, then provide the results of a method validation study for the primary manufacturing site and the results of the method transfer studies for the other sites. If the specifications are not the same at each site, then provide the results of separate validation studies for each method and include comparison test results from each testing site for the same set of lots. Also, justify why different set of specifications are warranted at different sites.
   (c) For each analytical method used at each site, provide the method number, the version and the effective date.
   (d) For each analytical method, revise the description to include a history of revisions.
   (e) (b) (4)
   (f) Since the method validation studies were performed in 1994-1996, the analytical methods, the release specification criteria, and the USP <1225> requirements for ruggedness and robustness have been significantly revised. The validation studies for each non-compendial method should be updated to address the current analytical ranges and to meet the current requirements of USP <1225>. These studies should include copies of example spectra and/or chromatograms for the reference samples, the typical samples and the blank. The system suitability criteria in each chromatographic method should be supported by the results from their method validation studies. Accordingly, provide the data.

4. The tabulated batch analysis data in section 3.2.S.4.4 does not support the proposed criteria for (b) (4) water content. Please revise these criteria to reflect the level observed in a typical lot, or provide additional justification.

5. Provide any additional available stability data on lots from each of the manufacturing sites.

DRUG PRODUCT

6. Regarding the drug product manufacturing process:

   (a) Provide a list of the specific manufacturing equipment to be used in the tablet manufacturing process.
   (b) Specify the acceptance criteria for percent yield in each manufacturing step.

7. Identify the contact laboratories which will perform testing on excipients, intermediates or finished tablets.

8. Regarding the excipient specifications:

   (a) Identify the tests which characterize the proposed Hypromellose (b) (4)

(b) Identity the tests which characterize the proposed Microcrystalline Cellulose (b) (4)

(c) Identify the tests which characterize the proposed Polyethylene Glycol (b) (4)

(d) Provide a brief description of the preparation (b) (4)

9. Regarding the analytical method information:

(a) Provide copies of representative spectra and/or chromatograms for the sample, reference standards, and blank for each analytical method.

(b) Since the method validation studies were performed in 1994-1996, the USP <1225> requirements for ruggedness and robustness have been revised. Update the method validation studies for the assay, dissolution and related compounds methods to address the effects of variations in the method and to support the proposed system suitability criteria. Accordingly, provide the results.

10. Provide a letter of authorization for each of the packaging component suppliers and for the materials of construction for these components.

11. Regarding the submitted stability information:

(a) Provide any additional room temperature stability data to support the proposed expiration date (b) (4)

(b) Either revise the storage statement to use the USP controlled room temperature statement or provide data to address the stability of drug product when stored at low temperature.

In addition, a deficiency letter has been submitted to the agent for DMF 10,867. These deficiencies must be resolved before the application can be approved.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Ravi Harapanhalli

2/28/2008 04:07:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/Reviewable Unit-CMC

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product:	Ferriprox® (deferiprone) 500 mg Film-Coated Tablet
Date of Submission:	September 26, 2007
Date of Receipt:	September 27, 2007
Our Reference Number:	NDA 21-825
Reviewable Unit:	CMC

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be March 27, 2008.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed (both electronic and paper) submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Hyon Z Lee

10/2/2007 03:55:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/Reviewable Unit-Clinical Pharmacology

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product:	Ferriprox® (deferiprone) 500 mg Film-Coated Tablet
Date of Submission:	September 26, 2007
Date of Receipt:	September 27, 2007
Our Reference Number:	NDA 21-825
Reviewable Unit:	Clinical Pharmacology

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be March 27, 2008.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed (both electronic and paper) submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Hyon Z Lee

10/2/2007 03:51:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/Reviewable Unit-PT

INFORMATION REQUEST LETTER

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your December 21, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox®(deferiprone).

We also refer to Study Title APO-066: 52 week oral (gavage) toxicity study in the iron-loaded and non-iron-loaded Sprague Dawley Rat, (b) (4) Study No: PC-02-09.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your Reviewable Unit.

During review of the 52 week rat study it became apparent that an area of concern was not addressed in the study report. An unusual number of animals that had received Ferriprox, naïve and iron-loaded, were reported to have malignant tumors. Some animals had multiple tumors and some with metastatic tumors. This information was only reported in the appendix containing the raw data line listings of the histopathology report. The tumor incidence data was not presented in tabular form and was not addressed in the manuscript of the report.

1. Please have the pathologist address this issue, and present a tabular summary of tumor incidence and discussion of the significance of the findings relating to nonclinical safety of the test article.

2. Please have the pathologist evaluate and discuss whether this is considered a preliminary predictor of critical findings that may be expected in lifetime carcinogenicity studies in view of the agency's concerns with these findings.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, R.N., MSN, RAC
RPM Team Leader
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Alice Kacuba

9/18/2007 11:43:04 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-825/Reviewable Unit-PT

Cato Research Ltd.
Attention: Lynda Sutton
US Agent for ApoPharma Inc.
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) for Ferriprox®(deferiprone) 500 mg Film-Coated Table (b) (4) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to your December 21, 2006 reviewable unit (RU) for the Pharmacology and Toxicology portion of your NDA.

We have completed our review of this RU and request the following studies:

1. An electrophysiology study in hERG cells.

2. Lifetime carcinogenicity studies.

3. Fertility and early embryonic development study in rats to evaluate male and female fertility and general reproductive performance.

We are providing these comments to you before we complete our review of the complete application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, R.N., MSN, RAC
RPM Team Leader, Hematology
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Alice Kacuba

6/21/2007 02:03:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-825/RUP-001

Cato Research
Attention: Lynda Sutton
U.S. Agent for ApoPharma
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product: Ferriprox® (deferiprone) 500 mg Tablet (b) (4)

Date of Submission: December 21, 2006

Date of Receipt: December 22, 2006

Our Reference Number: NDA 21-825

Reviewable Unit: RUP-001

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be June 22, 2007.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed (both electronic and paper) submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me, at (301) 796-2192.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Hyon Z Lee

1/10/2007 03:28:23 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 15, 2006
Time: 9:00-10:30 AM
Location: White Oak, Conference Room 1421

Application: IND 45,724; deferiprone

Type of Meeting: Pre-NDA Meeting

Meeting Chair: Dwaine Rieves, M.D.

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Medical Imaging and Hematology Drug Products

Dwaine Rieves, M.D., Deputy Division Director
George Shashaty, M.D., Medical Officer
Alice Kacuba, R.N., R.S.N., R.A.C., Regulatory Project Manager

Division of Clinical Pharmacology 5

Young-Moon Choi, Ph.D., Biopharmaceuticals Team Leader

Office of Oncology Drug Products
Rick Pazdur, M.D., Office Director
Karen Weiss, M.D., Deputy Office Director

External Constituent Attendees and Titles:

ApoPharma
John Connelly, Ph.D., Director, Regulatory Affairs and Nonclinical Development
Tonya Konovalenko, M.Sc., R.A.C., Manager, Regulatory Affairs
Dudley Pennell, M.D., Professor of Cardiology, National Heart and Lung Institute, Imperial College
Dian Shaw, R.N., Manager, Clinical Research
Michael Spino, B.Sc. Phm, Pharm.D., President
Fernando Tricta, M.D., Vice President, Medical Affairs
Yu-Chung Tsang, B.Sc., Ph.D., Chief Scientific Officer, Biopharmaceutics-Biostatistics

Cato Research
Haley Best, B.A., Project Coordinator
Allen Cato, Ph.D., President and Chief Executive Officer
Jeremy Cromer, B.A., Regulatory Submissions Specialist

Nadine Desautels, M.Sc., Scientist
Pascal Guibord, M.Sc., Biostatistician
Frank Pietrantonio, Ph.D., Scientist
Lynda Sutton, B.Sc., Chief Regulatory Officer
Vicki Tibbs, Ph.D., R.A.C., Senior Regulatory Scientist

Background:
The product under this IND is being investigated as a metal chelator for iron overload. Cato submitted a Pre-NDA Meeting Request on March 9, 2006 and a subsequent Background Package submitted April 17, 2006 which included questions to be addressed by the Agency. IND (b) (4) has been granted Fast Track Status and accepted into the Continual Marketing Application, Pilot 1 program. ApoPharma plans to submit a rolling submission beginning in July 2006.

Summary of Discussion of Meeting Package Questions:

On Thursday, 11 May 2006 the Division provided a set of written responses via facsimile to the sponsor, which were used to guide the discussions in today's meeting. The Sponsor's questions are in normal font, the FDA written responses are in bolded font, and meeting discussions are in italicized font.

Question 1
Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?

FDA response:
The four controlled trials (LA-01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.

- **All studies included only patients with β-thalassemia**
- **The prospective studies (LA-01, LA08-9701, and LA16-0102) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12-9907 was a retrospective trial.**
- **The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.**
- **The determination of clinical efficacy is a review issue.**
- **At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA-01, LA08-9701, LA16-0102.**

Meeting Discussion

ApoPharma stated that in reviewing the FDA responses, it was noted that additional clarification and information should be provided to FDA regarding the availability and adequacy of data to support the Ferriprox marketing application. Please see attached slides presented by ApoPharma that were used during the course of the meeting.

FDA asked if protocols are available for any of the studies described in the cited publications, including data from patients with β-thalassemia, sickle cell disease, or myelodysplastic syndromes. ApoPharma responded that protocols are available for some of these studies/publications. FDA responded that clinical studies supporting safety and efficacy would need to be submitted to the NDA and the submission should include protocols, statistical analysis plans (SAPs), and final study These expectations would also apply to published clinical studies that are intended to supply important clinical data..

ApoPharma referred the FDA to Question 1, in which the agency stated that LA12-9907 is a retrospective study. ApoPharma explained that LA12-9907 was conducted at the request of the EMEA. ApoPharma noted that a protocol for LA12-9907 was prepared prospectively and approved by the EMEA prior to the selection of patients, and the collection and analysis of the data.

Regarding the use of MRI T2 as a measure of efficacy and of clinical benefit, Dr. Pennell gave a brief description of the MRI T2* technology and its relationship to tissue iron concentration. ApoPharma explained that changes in T2* values are driven by changes in tissue iron concentration. ApoPharma explained the relationship between cardiac MRI T2* and left ventricular ejection fraction (LVEF) and the reproducibility of the T2* results.*

FDA asked for clarification on the liver iron concentration of the samples used for the validation of the liver MRI T2 measurements. ApoPharma responded that those questions would be addressed in a future submission to the IND (see attached slides) and the NDA.*

ApoPharma introduced data from study LA16-0102, a prospective, randomized ApoPharma-sponsored study. ApoPharma indicated the results of this study showed a superiority of deferiprone over deferoxamine in the ability to increase T2 and left ventricular ejection fraction. FDA noted that LA16-0102 used a 100mg/kg total daily dose; most other studies used a 75mg/kg dose. ApoPharma confirmed FDA's statement and stated that it will be seeking approval for doses between 75 and* (b) (4) (b) (4)

FDA asked if the demonstrated changes in T2 and LVEF in LA16-0102 are clinically meaningful. ApoPharma stated that while the exact correlation between heart iron concentration and clinical benefit has not been established, the changes demonstrated in LA16-0102 are considered clinically meaningful. ApoPharma stated that thalassemia*

patients by nature of their chronic anemia have higher ejection fractions than the normal population. ApoPharma noted that a small change (i.e. 3 to 5%) in left ventricular ejection fraction can translate to large (i.e. 40 to 50%) difference in mortality in patients.

FDA asked which study ApoPharma feels is the single most persuasive clinical study that will support the Ferriprox marketing application. ApoPharma responded that Study LA16-0102 is the most important study because it is prospective and randomized, and because it includes state of the art, validated measurements on the most critical manifestation of iron overload, i.e. cardiac iron accumulation. ApoPharma indicated that the liver iron concentration does not correlate with the cardiac iron concentration in patients undergoing chelation therapy. ApoPharma indicated the marketing application would rely on Study LA16-0102 and use Study LA12-9907 as a possible pivotal study as well.

FDA stated that Study LA12-9907 is not what is traditionally accepted as a prospective study, but might meet the level of a pivotal study if scientific rigor had been applied in its conduct and the data are as robust as ApoPharma has indicated. ApoPharma reiterated that Study LA12-9907 was prospectively defined and shows clinical benefit.

FDA inquired about the GCP compliance of Study LA16-0102. ApoPharma responded that Study LA16-0102 is compliant with GCP, that a prospective SAP was prepared, and they have access to case report forms from this study. ApoPharma noted that LA-01 would not stand up to a GCP audit because one of the reasons this study was terminated early was due to investigator non-compliance. ApoPharma noted that it believes that Studies LA16-0102, LA12-9907, and LA08-9701 would stand up to a GCP audit.

FDA asked if Study LA16-0102 was used to establish efficacy by the EMEA. ApoPharma stated that at the time of the Ferriprox submission to the EMEA, the MRI T2 technology was not available. ApoPharma explained that Study LA12-9907 was conducted as a post-marketing commitment, and upon the submission of the LA12-9907 results and other post-marketing information Ferriprox gained full approval by the EMEA.*

FDA asked how "worsening of existing cardiac disease" was defined in LA12-9907. ApoPharma replied that a cardiologist who was blinded to the chelation therapy the patient had received used the New York Heart Association classification to determine worsening or improvement of the patient's cardiac condition.

FDA pointed out that in this study there was no difference in left ventricular ejection fraction between deferiprone and deferoxamine. ApoPharma noted that Study LA12-9907 was not designed to assess the left ventricular ejection fraction but instead was designed to assess the occurrence of cardiac disease and survival. In Study LA12-9907, the left ventricular ejection fraction was evaluated by a number of cardiologists over time and was performed by echocardiogram, not by cardiovascular magnetic resonance (CMR). Dr. Pennell further explained that CMR was used in Study LA16-0102 and is highly reproducible while echocardiogram is less so. Dr. Pennell added that there is a poor relationship between ejection fraction and New York Heart Association

classification. FDA noted that both echocardiogram and CMR were apparently used in LA16-0102 and the results supposedly consistent between the two measures. Dr. Pennell noted CMR is more reproducible than echocardiograms for ejection fraction, therefore the congruency of the data in LA16-0102 is encouraging.

ApoPharma stated, despite the lack of prognostic value of liver iron concentration, the efficacy of Ferriprox in controlling the liver iron concentration was evaluated by applying the criteria used by Novartis to determine the success of treatment with Exjade. ApoPharma indicated the analysis of the data indicated that Ferriprox performed as well as or better than Exjade, based on the Novartis criteria for success and its use was associated with a 70% success rate. FDA asked whether the liver iron concentration was measured by SQUID or by liver biopsy in this analysis. ApoPharma responded that for most studies SQUID was used to determine liver iron concentration. In LA08-9701 and LA16-0102, all measurements were taken using SQUID. In LA-01 and LA-03, liver biopsies were taken in the event that a patient could not undergo SQUID. ApoPharma stated that the exact numbers of patients evaluated using SQUID and liver biopsy would be provided in a future submission and noted that all the liver iron concentration data measured by SQUID or biopsy will be submitted in the NDA.

Question 2

Does the FDA agree that the evidence of beneficial effect on cardiac morbidity and survival, supported by the efficacy endpoints of cardiac magnetic resonance imaging, serum ferritin levels and liver iron concentrations, are acceptable approaches for approval?

FDA Response:

- **Theoretically, these approaches could be acceptable**
- **The purported beneficial effect on cardiac morbidity and mortality is based on a retrospective, non-randomized trial (Borgna-Pignatti). The summarized data do not provide validation of an increase in cardiac MRI T2* as a surrogate of a clinically meaningful endpoint for the efficacy of deferiprone. The statistical differences noted in the supporting studies may not be clinically significant. Changes in serum ferritin levels are difficult to interpret because serum ferritin is subject to variations induced by a number of mechanisms that are unrelated to total body iron stores. Change in LIC using liver biopsy has generally been considered to be the standard measure of efficacy in response to iron chelation therapy, and only a fraction of patients in your trials had assessments of LIC by biopsy.**

Meeting Discussion

ApoPharma acknowledged that the issues pertaining to Question 2 were addressed during discussion of Question 1.

Question 3
For the Borgna-Pignatti et al. epidemiology study (2005), does the FDA agree that the submission of the literature publication, statistical report, and data listings will be sufficient for the evaluation of efficacy?

FDA Response:
You can submit the information. However, these data cannot be used to establish or support efficacy. If you submit the information, you will need to submit the protocol and all protocol amendments. All of the data collected in the study should be submitted to the NDA.

Meeting Discussion:
ApoPharma introduced the epidemiology study published by Borgna-Pignatti. Et. al. and noted survival data for this study included thalassemia patients that were born after 1970, and that had no heart disease at the start of the study. ApoPharma noted that an SAP was prospectively prepared for this study and was submitted to FDA prior to analysis of the data, but no comments were received. ApoPharma confirmed that the database for this study is available and can be submitted in the NDA.

ApoPharma confirmed that it believes Study LA16-0102 and the Borgna-Pignatti epidemiology study are the strongest studies supporting the efficacy of the Ferriprox application. ApoPharma stated that while they believe the epidemiology study is strong and supportive of the efficacy of Ferriprox, they are not seeking a mortality claim on the basis of the results of this study.

ApoPharma confirmed that the Borgna-Pignatti database to be included in the NDA will include data on disposition, exposure, demographics and efficacy.

Question 4
Does the FDA agree that the collective clinical data on the safety of deferiprone are appropriate and sufficient for evaluation of the safety of deferiprone?

FDA Response:
No. All data on all postmarketing reports of adverse events should be submitted to the NDA. In addition, all reports of serious adverse events associated with the administration of deferiprone up to the completion of the review of the NDA should be submitted to the Division. In regard to patients with neutropenia or agranulocytosis, a case report form should be submitted for each patient.

Meeting Discussion:
ApoPharma suggested the totality of the data collected in the prospectively controlled clinical study LA16-0102 and the supportive studies, LA12-9907 and LA08-9701 in combination with the prospectively defined analysis of retrospective data collected in the Borgna-Pignati study will be sufficient to support the clinical benefit of Ferriprox in a marketing application. FDA noted that the majority of this information has not been submitted to the IND.

ApoPharma indicated the marketing application will include all data on all post marketing reports of adverse events, including CRFs for all subjects who experienced neutropenia or agranulocytosis in clinical trials, and the narratives of both clinical, and post marketing spontaneous reports.

FDA stated that the NDA should highlight any unresolved cases of agranulocytosis or deaths. ApoPharma noted that they are aware of the risk associated with agranulocytosis, and have therefore closely monitored all cases and convened an international committee of experts to determine how to identify at-risk patients.

Question 5
Does the Agency agree with the plan for Module 2, Sections 2.7.3 and 2.7.4, and that a separate Integrated Analysis of Efficacy (i.e., Module 5, Section 5.3.5.3.1) and Integrated Analysis of Safety (i.e., Module 5, Section 5.3.5.3.2) will be prepared?

FDA Response:
Yes.

Meeting Discussion
There was no further discussion on this topic.

Question 6
Ferriprox is being developed for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy. Does the FDA agree with the proposed indication statement?

FDA Response:
No. The submitted data include studies performed in patients with β-thalassemia almost exclusively. The indication, if approved, will reflect the population enrolled in the trials.

Meeting Discussion
FDA stated the final indication would be determined based on the information provided in the marketing application.

Question 7
At the pre-NDA meeting on 09 July 2004, ApoPharma reached an agreement with the Agency to submit a continuous marketing application (a rolling NDA). A revised schedule of tentative submission dates for reviewable units (RUs) prepared in eCTD format is provided in Section 4.1 of this package. Does the Agency agree that the proposed schedule for submission of the RUs is acceptable?

FDA Response
Yes.

Meeting Discussion
There was no further discussion on this topic.

Question 8
In Version 1.1 of the Study Data Specifications, dated 18 March 2005, it is recommended that data definition files be submitted as define.xml files using the Clinical Data Interchange Standards Consortium (CDISC), Version 3.1, recommendations. ApoPharma has prepared all data definition files (i.e., define.pdf) in accordance with the Agency's recommendations for eNDAs, outlined in the FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format—NDA, dated 1999, and CDISC, Version 3.1, recommendations. Is submission of data definition files as define.pdf instead of define.xml acceptable?

FDA Response
For CDISC/SDTM data, DEFINE.XML is preferred, but DEFINE.PDF is acceptable. For analysis files, DEFINE.PDF is preferred.

Meeting Discussion
There was no further discussion on this topic.

Question 9
All clinical study reports have been prepared in accordance with the Guidance document Providing Regulatory Submissions in Electronic Format–NDAs (dated January 1999) as separate PDF files. These study report files include all appendices as defined in the ICH E3, Structure and Content of Clinical Study Reports (July 1996), except for case report forms and individual patient data listings (case report tabulations). ApoPharma intends to provide all clinical study reports, including study reports from "pivotal" studies as legacy reports, in its NDA in eCTD format. Does the Agency agree with this approach?

FDA Response
This is acceptable.

Meeting Discussion
There was no further discussion on this topic.

Question 10
According to the Guidance document Providing Regulatory Submissions in Electronic Format–NDAs, dated January 1999, the need for patient profiles depends on the indication; they may not be needed at all or may be needed only for patients who discontinued or had a serious adverse event (SAE). Please confirm whether patient profiles should be included in the submission, and if so, for what patients.

FDA Response

Patient profiles should be submitted for all patients in any of the trials who died, suffered a serious AE, discontinued study drug because of an AE or were discontinued from any trial for any reason. Case report forms should be submitted for all deaths, AEs, and any withdrawal from the study because of AEs. All discontinuations should be presented fully and the reason for discontinuation explained.

Meeting Discussion

ApoPharma requested clarification of the FDA's response to Question 10. FDA confirmed that ApoPharma needs to plan to submit case report forms for serious adverse events. FDA indicated that if concerns arise during review regarding adverse events, submission of those case report forms will be requested as well.

ApoPharma stated that all cases of neutropenia observed in clinical trials were classified as serious adverse events, irrespective of the severity of the decline of the neutrophil count or its clinical severity. A complete analysis and discussion of incidence trends for cases of agranulocytosis and neutropenia will be included in the safety section of the NDA.

Additional FDA comments

General Considerations

- **Some of the studies terminated earlier than expected. Provide an explanation for those terminations.**
- **All Foreign postmarketing experience data should be submitted in the NDA.**
- **Provide a clear presentation of the efficacy and safety of deferiprone based on comparisons to control groups (including historical controls where concurrent controls are not available).**
- **We are concerned that your database may not satisfy the regulatory requirements for "adequate and well controlled" trials. Additionally, data from retrospective studies are generally not adequate for approval of a drug.**
- **The statistical analysis plans for the various trials are not clearly delineated. Comparative trials between deferiprone and deferoxamine should be either superiority or non-inferiority in design. If a non-inferiority design is selected, the effect size of the standard therapy must be well established in order to determine the delta margin. The effect size of deferoxamine is not well characterized. A preliminary review of the comparative studies submitted indicates that deferiprone is not superior to deferoxamine in reducing serum ferritin. It is not possible to assess the non-inferiority of deferiprone compared to deferoxamine from the data and analyses provided.**
- **Since many of the patients in the target population are of pediatric age, it is advisable to analyze subsets of the pediatric population for efficacy and safety.**
- **The variability of protocol specified endpoints for the different studies will complicated the review for determining the efficacy of deferiprone.**

Labeling

- **Regarding your proposed labeling, please submit the labeling in the PLR format.**

CMC

- **Please request a pre-NDA CMC Meeting and provide a background package for the meeting.**

Electronic

- **Technical questions and details on the sample submission process can be directed to:** ESUB@CDER.FDA.GOV

Biopharm

- **Please include the raw data analyzed for PK in your NDA.**

Additional meeting discussions

ApoPharma addressed FDA's question regarding early termination of studies during discussion of Questions 1 and 2 stating that LA-01 was terminated early partially due to investigator non-compliance. ApoPharma added that the decision to terminate LA-01 was a difficult one for all involved parties.

FDA noted ApoPharma may have enough information to support the filing of a marketing application for Ferriprox. ApoPharma reminded FDA that there are data available from prospective, randomized trials that the FDA has not seen. ApoPharma requested guidance from the FDA regarding what is needed and how it should be submitted. FDA instructed ApoPharma that the NDA should highlight the pivotal studies that ApoPharma is proposing (including any studies undergoing reanalyses) to support the marketing approval for deferiprone.

FDA expressed concern that, based on the discussion, significant amounts of information have not been submitted to the IND therefore, based on the limited data provided the NDA database did not appear to be typical. Again the FDA reiterated the need for ApoPharma to organize the NDA highlighting the pivotal studies that they were relying upon for marketing approval.

FDA indicated its understanding was that ApoPharma has proposed that the efficacy of the marketing application will be supported by Study LA16-0102 as an adequate and well controlled study in addition to supporting studies including the Borgna-Pignatti epidemiology study and LA12-9907. ApoPharma acknowledges that drawing support for the NDA from only one well-controlled study is not typical, but may be justified.

Meeting Prepare: Alice Kacuba

Chair Concurrence: Dwaine Rieves, M.D.

ApoPharma Inc.

Ferriprox (deferiprone)

15 May 2006
Type B Meeting

CATO RESEARCH

Meeting Questions – Clinical

- **Question 1**
  - *Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?*
- **FDA Response**
  - The four controlled trials (LA01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.
    - All studies included only patients with β–Thalassemia
    - The prospective studies (LA01, LA08, and LA16) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12 was a retrospective trial
    - The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.
    - The determination of clinical efficacy is a review issue.
    - At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA01, LA08, LA16

CATO RESEARCH

Meeting Questions – Clinical

- **Question 1**
  - *Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?*
- **FDA Response**
  - The four controlled trials (LA01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.
    - **All studies included only patients with β–Thalassemia**
    - The prospective studies (LA01, LA08, and LA16) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12 was a retrospective trial
    - **The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.**
    - The determination of clinical efficacy is a review issue.
    - At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA01, LA08, LA16

CATO RESEARCH 3 CONFIDENTIAL Copyright © 2006. Cato Research Ltd.

Summary of Clinical Studies with Deferiprone/Ferriprox in Potential Indications

- Approximately 150 iron-loaded patients with a disease other than β-thalassemia major were treated with deferiprone
  - Thalassemia intermedia (n = 17)
  - Hb E-β-thalassemia (n = 32)
  - Sickle cell disease (n = 26)
  - Myelodysplastic syndromes (n = 41)
  - Other transfusional iron overload conditions (n = 29)
- Efficacy and safety results were very similar to those in β-thalassemia major patients:
  - Serum ferritin levels and LIC, when investigated, decreased or stabilized over time in all studies
  - Deferiprone was generally well tolerated
  - Adverse events experienced were similar to those of β-thalassemia major patients (few incidents of agranulocytosis, neutropenia, and gastrointestinal symptoms)

CATO RESEARCH 4 CONFIDENTIAL Copyright © 2006. Cato Research Ltd.

Meeting Questions – Clinical

- **Question 1**
  - *Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?*
- **FDA Response**
  - The four controlled trials (LA01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.
    - All studies included only patients with β–Thalassemia
    - **The prospective studies (LA01, LA08, and LA16) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12 was a retrospective trial**
    - The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.
    - The determination of clinical efficacy is a review issue.
    - At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA01, LA08, LA16

CATO RESEARCH

Ferriprox (Deferiprone)

Clinical Program	n*		Drug Exposure (patient-years)*	
Randomized with Desferal (LA01)	35		61	
Safety and efficacy (LA02)	187		168	
Compassionate use (LA03)	25		49	
Compassionate use (LA04)	78		98	
Safety and efficacy (LA06)	160*		497	
Alternate use with Desferal (LA08)	29		29	
Clastogenicity Study (LA10)	20*		2	
Safety and efficacy (LA11)	24	1,174	28	2,116
Heart disease and survival (LA12)	54*		294*	
PK profile in cirrhosis (LA14)	6*		-	
Safety and Efficacy (LA15)	29		7	
Safety and Efficacy (LA16)	29		27	
Active Surveillance Program (LA17)	532		1154	
Bioavailability (LA20)	15		-	+
Bioequivalence (LA21)	42		-	

Patients not re-counted

- **Post-Marketing Ferriprox exposure (49 countries) 12,101 = 14,217**
- **> 400 publications in the scientific literature. Estimated use in >7500 patients, 1-85 years old, some of them for > 14 years**

Pre-Approval Meeting With EMEA

- Requested confirmation of efficacy on clinical outcome on cardiac disease
- Protocol on the analysis of occurrence of cardiac disease/worsening of cardiac disease in patients treated long-term with Ferriprox vs deferoxamine in one single center reviewed and approved by EMEA prior to collection of data (LA-12).

Meeting Questions – Clinical

- **Question 1**
  - *Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?*
- **FDA Response**
  - The four controlled trials (LA01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.
    - All studies included only patients with β–Thalassemia
    - The prospective studies (LA01, LA08, and LA16) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12 was a retrospective trial
    - **The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.**
    - The determination of clinical efficacy is a review issue.
    - At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA01, LA08, LA16

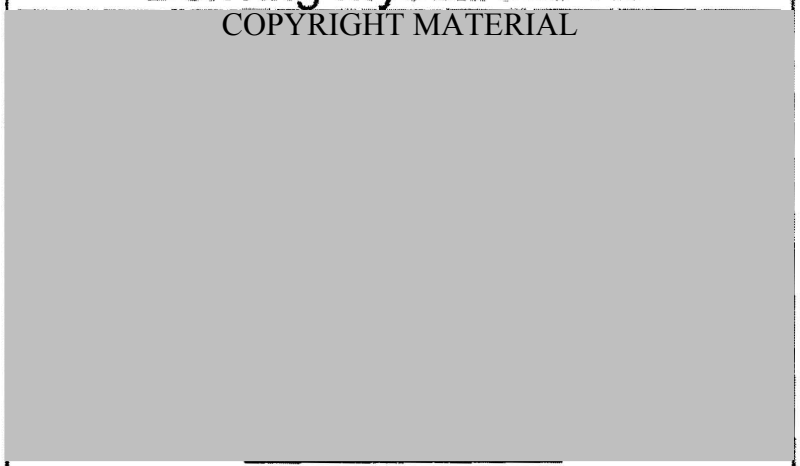
CATO

8

Assessing the Efficacy of Iron Chelation

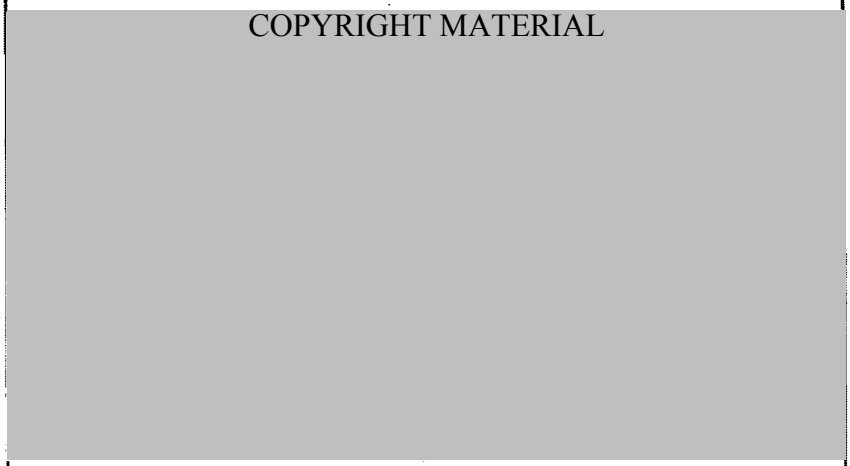
- Iron-induced cardiac disease causes 70% of deaths in transfusion-dependent thalassemia.
- The objective of iron chelation therapy in those patients is to prevent iron-induced organ damage and premature death
- Measures of cardiac iron have not been available until recently

Deriving Myocardial T2*



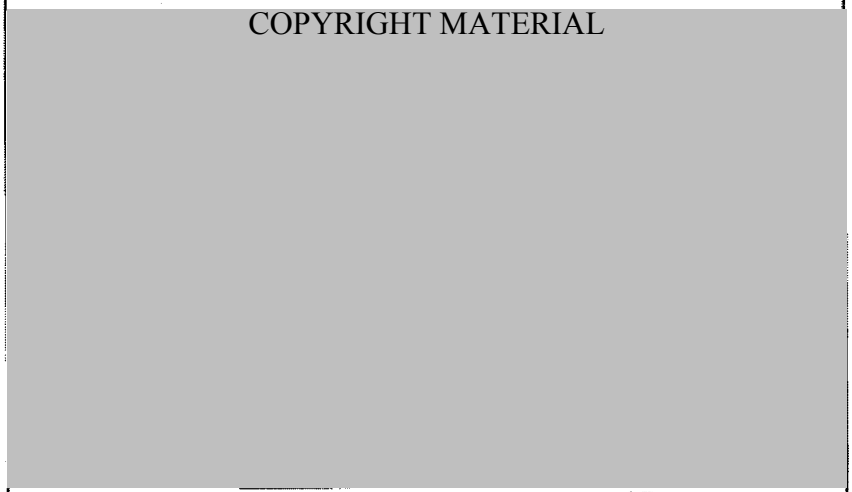
Anderson LJ. Eur Heart J 2001; 22: 2171-9

Ln [Liver Iron] vs Ln [Liver T2*] - Humans



Anderson LJ. Eur Heart J 2001; 22: 2171-9

Heart Iron vs T2* - Gerbils

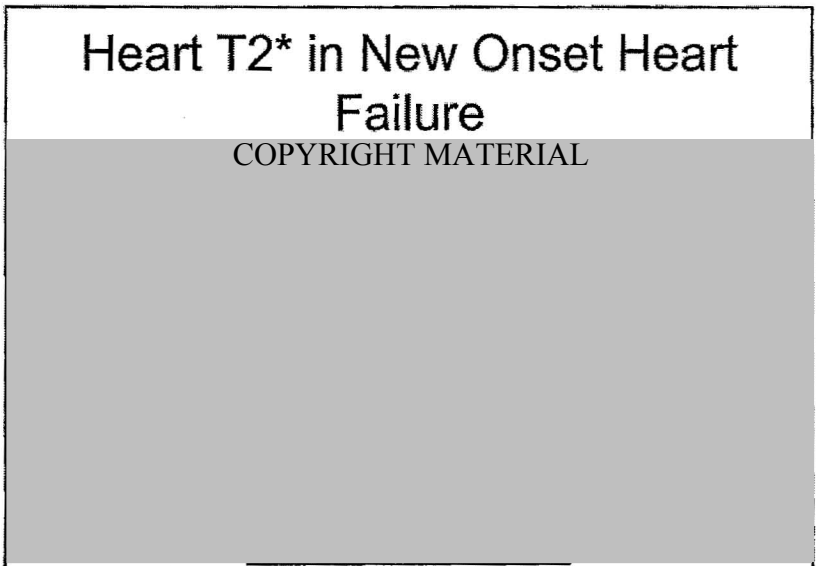


Wood JC. Circulation 2005; 112: 535.

Heart T2* vs LV Ejection Fraction

Anderson LJ. Eur Heart J 2001; 22: 2171-9

Heart T2* in New Onset Heart Failure

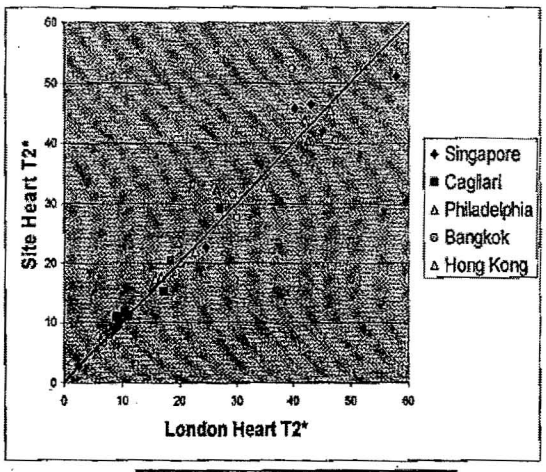


Tanner M. ASH Abstracts 2005

Heart T2* Interstudy Reproducibility

Westwood. J Cardiovasc Magn Reson 2002; 4: 172.

Heart T2* - International Reproducibility



5 sites

50 patients

Heart CoV 5.9 %

NIH Funded: R01 DK066084-01

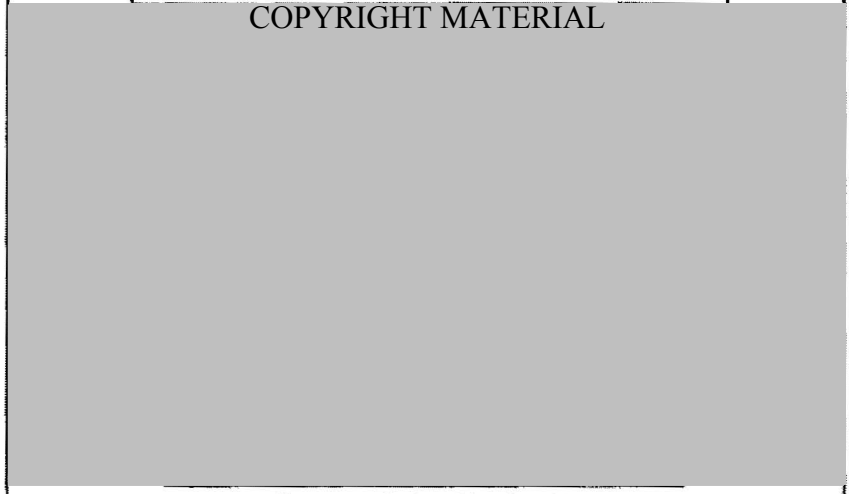
Evaluating the Efficacy of Iron Chelators

Cardiac Iron Concentration

Randomized controlled trial of deferiprone or deferoxamine in β-thalassemia major patients with asymptomatic myocardial siderosis
Pennell et al, Blood 2006 (LA-16)

Evaluating the Efficacy of Iron Chelators

Cardiac Iron Concentration



Pennell DJ et al. Blood 2006

Evaluating the Efficacy of Iron Chelators

Cardiac Function

Pennell DJ et al. Blood 2006

Pre-Approval Meeting With EMEA

- Requested confirmation of efficacy on clinical outcome on cardiac disease
- Protocol on the analysis of occurrence of cardiac disease/worsening of cardiac disease in patients treated long-term with Ferriprox vs deferoxamine in one single center reviewed and approved by EMEA prior to collection of data (LA-12).

Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis

ANTONIO PIGA, CARMEN GAGLIOTI, EUGENIA FOGLIACCO, FERNANDO TRICTA

haematologica/journal of hematology vol. 88(05):may 2003

Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis

ANTONIO PIGA, CARMEN GAGLIOTI, EUGENIA FOGLIACCO, FERNANDO TRICTA

haematologica/journal of hematology vol. 88(05):may 2003

Kaplan Meier Survival Curves of Thalassemia Patients by Cohort of Birth (N=977)

Age (Yr)

Borgna-Pignatti et al, 2004

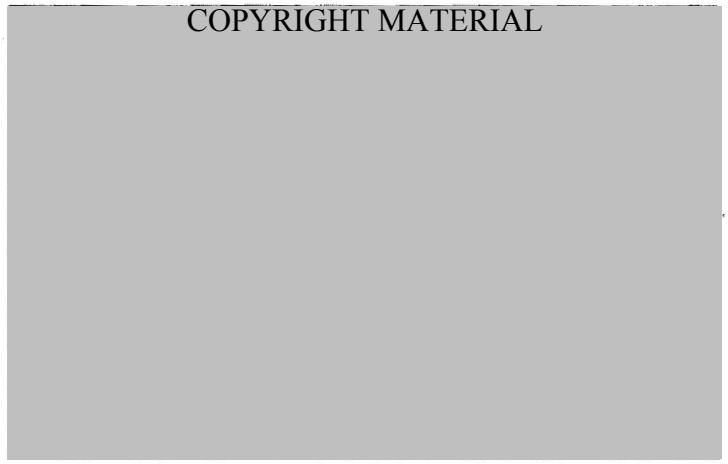
Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major

Borgna-Pignatti et al, Blood 2006

Deferoxamine-only group: 359 patients treated with DFO before Jan 1995 and during the entire study period

Deferiprone-switched group: 157 patients treated with DFO at least until Jan 1995 and switched to deferiprone at some point after Jan 1995 (median deferiprone treatment duration 4yr)

Incidence of cardiac events by calendar year



Distribution of Cardiac Events by Treatment Groups

Cardiac Event	DFO-only (n = 359)	DFP-switched (n = 157)	P-value
Death due to cardiac cause	15	0	0.001
Heart failure	30	0	
Arrhythmia	12	0	

Assessing the Efficacy of Iron Chelation
Liver Iron Concentration (LIC)

Reference	Duration	Chelator	N	Liver Iron Conc. mean ± SD	
				Initial	Final
ApoPharma LA-01	3 years	DFP 75 mg/kg/d	13	8.5 ± 3.6 mg/g dw	8.9 ± 2.8 mg/g dw
		DFO 50 mg/kg; 5d/wk	15	7.1 ± 4.1 mg/g dw	7.8 ± 4.7 mg/g dw
ApoPharma LA-03	Up to 4 years	DFP 75 mg/kg/d	19	17.0 ± 9.1 mg/g dw	11.3 ± 6.2 mg/g dw
ApoPharma LA-02	1 year	DFO 33 mg/kg; 2d/wk DFP 75 mg/kg/d; 5d/wk	29	1629±744 µg/g liver	1565±657 µg/g liver
		DFO 50 mg/kg; 5d/wk	38	1625±697 µg/g liver	1186±537 µg/g liver
ApoPharma LA-16	1 year	DFP 92 mg/kg/d	27	6.16±4.62 mg/g dw	5.24±N mg/g dw
		DFO 43 mg/kg; 6d/wk	30	6.32±5.77 mg/g dw	4.78±N mg/g dw

Assessing the Efficacy of Iron Chelation
Liver Iron Concentration (LIC)

Reference	Duration	Chelator	N	Liver Iron Conc. mean ± SD	
				Initial	Final
Maggio et al; 2002 (biopsy)	1 year	DFP 75 mg/kg/d	20	3.4 ± 5.4mg/g dw	2.3 ± 2.2mg/g dw
		DFO 50 mg/kg; 5d/wk	15	3.5 ± 3.0mg/g dw	1.8 ± 0.9mg/g dw
Fischer et al; 2003 (SQUID)	~2 years	DFP 73 mg/kg/d	54	1.5 ± 0.9mg/g liver	2.0 ± 0.9 mg/g liver
		DFO 30 mg/kg; 5d/wk	51	1.1 ± 0.6mg/g liver	1.3 ± 0.7mg/g liver
Peng et al; 2003 (biopsy)	3 years	DFP 75 mg/kg/d	11	141 ± 35 μ mol/g	99 ± 21 μ mol/g
		DFO 50 mg/kg; 5d/wk	10	115 ± 52 μ mol/g	83 ± 18 μ mol/g
Tondury et al; 1998	Up to 9 years	DFP 52-112 mg/kg/d	9	7.6 ± 4.4 mg/g mg/g dw (SQUID)	8.9 ± 5.6 mg/g mg/g dw (biopsy)
Mazza et al; 1998 (biopsy)	>1	DFP 70 mg/kg/d	20	18.1 mg/g dw	21.0 mg dw
Del Vecchio et al. (SQUID)	1.5	DFP 75 mg/kg/d	9	1690 μg/g liver	2305 μg/g liver

Exjade Primary Endpoint - Study 0107

- Primary endpoint: treatment success rate at 1 year
- Hypothesis: success rate in patients receiving ICL670 is non-inferior to deferoxamine

Treatment success criteria

LIC at baseline, mg Fe/g dw	Success, if LIC after 1 year, mg Fe/g dw
2 to < 7	Maintenance within 1 to < 7
≥ 7 to < 10	Decrease to within 1 to < 7
≥ 10	Decrease of ≥ 3

Success rate based on ICL670 primary efficacy success criteria

	Success rate (%) after 1 year of treatment	
LIC at baseline	ICL670 (N=276)	Ferriprox (N=60)
2-<7 mg Fe/g dw	34/85 (40%)	22/27 (81%)
≥7 mg Fe/g dw	112/191 (59%)	20/33 (61%)
Overall	146/276 (53%)	42/60 (70%)

Assessing the Efficacy of Iron Chelation

Serum Ferritin

Reference	Duration	Chelator	N	Serum Ferritin (µg/L) mean ± SD	
				Initial	Final
ApoPharma LA-01	2 years	DFP 75 mg/kg/d	21	1975 ± 1107	2192 ± 1092
		DFO 50 mg/kg; 5d/wk	20	2190 ± 1450	2294 ± 1251
ApoPharma LA-08	2 years	DFP 75 mg/kg/d	16	3863 ± 566	2716 ± 461
		DFO 20-50 mg/kg; 5d/wk	40	3480 ± 417	2819 ± 292
ApoPharma LA-16	1 year	DFP 100 mg/kg/d	29	1791 ± 1029	1610 ± 981
		DFO 50 mg/kg; 5d/wk	32	2795 ± 2441	2329 ± 2029
ApoPharma LA-02	1 years	DFP 75 mg/kg/d	187 (ITT)	2696 ± 1877	2633 ± 1815
ApoPharma LA-06	4 years	DFP 75 mg/kg/d	187 (ITT)	2696 ± 1877	2889 ± 1972
ApoPharma LA-05	7 years	DFO 50 mg/kg; 5d/w	187 (ITT)	2696 ± 1877	2963 ± 1965
ApoPharma LA-15	3 months	DFP 75 mg/kg/d	27	3364 ± 900	1271 ± 302

Assessing the Efficacy of Iron Chelation

Serum Ferritin

Reference	Duration	Chelator	N	Serum Ferritin (µg/L) mean ± SD	
				Initial	Final
Olivieri et al; 1998	>5 year	DFP 70 mg/kg/d	29	3748 (200-10000)	2550 (80-14500)
Hoffbrand et al; 1998	1-4 years	DFP 50-79 mg/kg/d	26	2937 (980-9090)	2328 (825-5970)
Cecil et al; 2002	3 years	DFP 75 mg/kg/d	181	2579 1687	2380 1600
Taher et al; 2001	2 years	DFP 75 mg/kg/d	16	3663 ± 566	2716 ± 461
		DFO 20-50 mg/kg; 5d/wk	40	3480 ± 417	2819 ± 292
Maggio et al; 2002	1 year	DFP 75 mg/kg/d	71	2283 ± 754	2061 ± 853
		DFO 50 mg/kg; 5d/wk	73	2019 ± 678	1787 ± 893
Fischer et al; 2003	~2 years	DFP 75 mg/kg/d	73	1897 ± 885	2116 ± 1402
		DFO 30 mg/kg; 5d/wk	30	1422 ± 795	1631 ± 951
Peng et al; 2003	3 years	DFP 75 mg/kg/d	11	4652 ± 2845	2792 ± 1482
		DFO 50 mg/kg; 5d/wk	10	4109 ± 2332	2612 ± 1585
Taher et al; 2005	2 years	DFP 100 mg/kg/d	12	3901 ± 3616	1790 ± 2205

Summary

- Deferiprone was superior to deferoxamine in removing iron from the heart in transfusion-dependent patients (LA-16)
- The data from the ApoPharma-sponsored studies and from the literature are consistent that deferiprone can reduce or stabilize the liver iron concentration and the serum ferritin values in transfusion-dependent patients
- Deferiprone was superior to deferoxamine in decreasing the incidence of iron-induced cardiac disease (LA-12 & Epidemiology Study)
- Deferiprone was superior to deferoxamine in increasing the survival of thalassemia major patients (LA-12 & Epidemiology Study)

Meeting Questions – Clinical

- **Question 1**
  - *Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?*
- **FDA Response**
  - The four controlled trials (LA01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.
    - All studies included only patients with β–Thalassemia
    - The prospective studies (LA01, LA08, and LA16) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12 was a retrospective trial
    - The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.
    - **The determination of clinical efficacy is a review issue.**
    - At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA01, LA08, LA16

CATO RESEARCH 35

Meeting Questions – Clinical

- **Question 1**
  - *Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?*
- **FDA Response**
  - The four controlled trials (LA01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.
    - All studies included only patients with β–Thalassemia
    - The prospective studies (LA01, LA08, and LA16) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12 was a retrospective trial
    - The use of changes in serum ferritin and in MRI T2* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.
    - The determination of clinical efficacy is a review issue.
    - **At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA01, LA08, LA16**

CATO RESEARCH 36

Meeting Questions – Clinical

- **Question 2**
  - *Does the FDA agree that the evidence of beneficial effect on cardiac morbidity and survival, supported by the efficacy endpoints of cardiac magnetic resonance imaging, serum ferritin levels and* liver iron concentrations, *are acceptable approaches for approval?*

- **FDA Response**
  - Theoretically, these approaches could be acceptable
  - The purported beneficial effect on cardiac morbidity an mortality is based on a retrospective, non-randomized trial (Borgna-Pignati). The summarized data do not provide validation of an increase in cardiac MRI T2* as a surrogate of a clinically meaningful endpoint for the efficacy of Deferiprone. The statistical differences noted in the supporting studies may not be clinically significant. Changes in serum ferritin levels are difficult to interpret because serum ferritin is subject to variations induced by a number of mechanisms that are unrelated to total body iron stores. Change in LIC using liver biopsy has generally been considered to be the standard measure of efficacy in response to iron chelation therapy, and only a fraction of patients in your trials had assessments of LIC by biopsy.

Meeting Questions – Clinical

- **Question 3**
  - *For the Borgna-Pignatti et al. epidemiology study (2005), does the FDA agree that the submission of the literature publication, statistical report, and data listings will be sufficient for the evaluation of efficacy?*

- **FDA Response**
  - You can submit the information. However, these data can not be used to establish or support efficacy. If you submit the information, you will need to submit the protocol and all protocol amendments. All of the data collected in the study should be submitted to the NDA

Question 3: Borgna-Pignatti et al. (2005)

- ApoPharma will provide the following information in the submission with regards to this study :
  - Protocol, which was a statistical analysis plan
    - Previously submitted to IND (22 March 05/SN 095, prior to analysis)
    - No amendments were made
  - Database including efficacy information
- ApoPharma agrees with the Division's comment – all data collected in this study will be submitted which includes:
  - Disposition
  - Exposure
  - Demographics
  - Efficacy

CATO RESEARCH 39

Meeting Questions – Clinical

- **Question 4**
  - *Does the FDA agree that the collective clinical data on the safety of deferiprone are appropriate and sufficient for evaluation of the safety of deferiprone?*
- **FDA Response**
  - No. All data on all postmarketing reports of adverse events should be submitted to the NDA. In addition, all reports of adverse events associated with the administration of deferiprone up to the completion of the review of the NDA should be submitted to the Division. In regard to patients with neutropenia or agranulocytosis, a case report form should be submitted for each patient.

CATO RESEARCH 40

Safety Information

- ApoPharma agrees with the Division's response and will include:
  - Clinical trial safety database
    - Meeting Package: Table 1.4-1 (SN: 0121/ page 020)
  - All postmarketing adverse events will be submitted to NDA
  - Safety update will be submitted
  - CIOMS for postmarketing (AERS)
  - CRFS for all neutropenia and agranulocytosis will be submitted

Meeting Questions – Clinical

- **Question 5**
  - *Does the Agency agree with the plan for Module 2, Sections 2.7.3 and 2.7.4, and that a separate Integrated Analysis of Efficacy (i.e., Module 5, Section 5.3.5.3.1) and Integrated Analysis of Safety (i.e., Module 5, Section 5.3.5.3.2) will be prepared?*

- **FDA Response**
  - Yes.

Meeting Questions – Clinical

- **Question 6**
  - *Ferriprox is being developed for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy. Does the FDA agree with the proposed indication statement?*

- **FDA Response**
  - No. The submitted data include studies performed in patients with β–thalassemia almost exclusively. The indication, if approved, will reflect the population enrolled in the trials.

Meeting Questions – eCTD Submission Schedule

- **Question 7**
  - *At the pre-NDA meeting on 09 July 2004, ApoPharma reached an agreement with the Agency to submit a continuous marketing application (a rolling NDA). A revised schedule of tentative submission dates for reviewable units (RUs) prepared in eCTD format is provided in Section 4.1 of this package. Does the Agency agree that the proposed schedule for submission of the RUs is acceptable?*

- **FDA Response**
  - Yes.

Question 7: eCTD Submission Schedule

- Biopharmaceutics Reviewable Unit: July 2006
- Pharmacology Reviewable Unit: August 2006
- CMC Reviewable Unit: September 2006
- Clinical/Statistical Reviewable Unit: November 2006

Meeting Questions – eCTD (CDISC Format)

- **Question 8**
  - *In Version 1.1 of the Study Data Specifications, dated 18 March 2005, it is recommended that data definition files be submitted as define.xml files using the Clinical Data Interchange Standards Consortium (CDISC), Version 3.1, recommendations. ApoPharma has prepared all data definition files (i.e., define.pdf) in accordance with the Agency's recommendations for eNDAs, outlined in the FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format—NDA, dated 1999, and CDISC, Version 3.1, recommendations. Is submission of data definition files as define.pdf instead of define.xml acceptable?*

- **FDA Response**
  - For CDISC/SDTM data, DEFINE.XML is preferred, but DEFINE.PDF is acceptable. For analysis files, DEFINE.PDF is preferred.

Meeting Questions – eCTD (CSR Granularity)

- **Question 9**
  - *All clinical study reports have been prepared in accordance with the Guidance document Providing Regulatory Submissions in Electronic Format–NDAs (dated January 1999) as separate PDF files. These study report files include all appendices as defined in the ICH E3, Structure and Content of Clinical Study Reports (July 1996), except for case report forms and individual patient data listings (case report tabulations). ApoPharma intends to provide all clinical study reports, including study reports from "pivotal" studies as legacy reports, in its NDA in eCTD format. Does the Agency agree with this approach?*

- **FDA Response**
  - This is acceptable.

Meeting Questions – eCTD (Patient Profiles)

- **Question 10**
  - *According to the Guidance document Providing Regulatory Submissions in Electronic Format–NDAs, dated January 1999, the need for patient profiles depends on the indication; they may not be needed at all or may be needed only for patients who discontinued or had a serious adverse event (SAE). Please confirm whether patient profiles should be included in the submission, and if so, for what patients.*

- **FDA Response**
  - Patient profiles should be submitted for all patients in any of the trials who died, suffered a serious AE, discontinued study drug because of an AE or were discontinued from any trial for any reason. Case report forms should be submitted for all deaths, AEs, and any withdrawal from the study because of AEs. All disontinuations should be presented fully and the reason for discontinuation explained.

Patient Profiles

- Patient Profiles
  - Withdrawals due to adverse events
  - Serious adverse events
  - All deaths
- Case Report Forms
  - All deaths
  - Withdrawals from study due to adverse events

FDA Additional Comments

FDA Additional Comments (1): Clinical/Stats

- *Some of the studies terminated earlier than expected. Provide an explanation for those terminations.*
- *All Foreign postmarketing experience data should be submitted in the NDA.*
- *Provide a clear presentation of the efficacy and safety of deferiprone based on comparisons to control groups (including historical controls where concurrent controls are not available).*
- *We are concerned that your database may not satisfy the regulatory requirements for "adequate and well controlled" trials. Additionally, data from retrospective studies are generally not adequate for approval of a drug.*

FDA Additional Comments (2): Clinical/Stats

- *The statistical analysis plans for the various trials are not clearly delineated. Comparative trials between deferiprone and deferoxamine should be either superiority or non-inferiority in design. If a non-inferiority design is selected, the effect size of the standard therapy must be well established in order to determine the delta margin. The effect size of deferoxamine is not well characterized. A preliminary review of the comparative studies submitted indicates that Deferiprone is not superior to deferoxamine in reducing serum ferritin. It is not possible to assess the non-inferiority of Deferiprone compared to deferoxamine from the data and analyses provided.*
- *Since many of the patients in the target population are of pediatric age, it is advisable to analyze subsets of the pediatric population for efficacy and safety.*
- *The variability of protocol specified endpoints for the different studies will complicated the review for determining the efficacy of Deferiprone.*

Overall Exposure to Deferiprone/Ferriprox*

Studies/Programs	Number of Subjects Enrolled (unique†)	Overall Exposure Total/Pediatric (Patient-Years)
ApoPharma-Sponsored Clinical Studies	323‡	804.75 / 255.04
ApoPharma-Sponsored Compassionate-Use	103	157.16 / 25.08
ApoPharma-Sponsored Pharmacokinetics	57 (healthy volunteers)	NAP
ApoPharma Supported - Investigator-Driven	LA-11: 24 Borgna-Pignatti (2005): 157§	21.99 / NA 750§ / NA
ApoPharma Supported - Ministry of Health Surveillance	532 (including 22 patients transferred from LA-04)	1,154.00
Total for All Studies	**1,174**	**2,887.90/≥280.14**
Worldwide Post-marketing	**NA**	**10,098.60**

NA = not available; NAP = not applicable.
* As per Table 7.2-1, Section 7.2.1, pre-NDA meeting information package dated 17 April 2006
† Patients enrolled in one study only
‡ All patients enrolled in only one study. All patients including exposed and not exposed to Ferriprox.
§ Patients enrolled in more than one study. Patients were counted only once for both patient and exposure calculations.

CATO RESEARCH 53 CONFIDENTIAL

FDA Additional Comments (3): Labeling, CMC, Electronic, Biopharm

- *Labeling*
  - *Regarding your proposed labeling, please submit the labeling in the PLR format.*
- *CMC*
  - *Please request a pre-NDA CMC Meeting and provide a background package for the meeting.*
- *Electronic*
  - *Technical questions and details on the sample submission process can be directed to:*
    - *ESUB@CDER.FDA.GOV*
- *Biopharm*
  - *Please include the raw data analyzed for PK in your NDA.*

CATO RESEARCH 54 CONFIDENTIAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 15, 2004
Time: 12:30-1:30 PM
Location: Parklawn Building, Room 6B-45

Application: IND 45,724

Type of Meeting: Type C meeting to discuss primary endpoint

Meeting Chair: George Shashaty

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Kathy Robie-Suh, M.D., Ph.D.; Deputy Division Director
George Shashaty, M.D.; Medical Team Leader, Hematology
Alice Kacuba, MSN, R.N., RAC; Regulatory Health Project Manager

External Constituent Attendees and Titles:
Apotex

Attendee	Title
Fernando Tricta	V.P. Medical Affairs
Graziella Soulban	Director, Clinical
John Connelly	Director, Pre-clinical
Sonia Sanhueza	Director, Regulatory Affairs
David Shoemaker	Consultant, CATO

Background:

IND 45,724; Ferriprox (deferiprone) Tablets is being investigated for the treatment of transfusion dependent iron overload. Pre-NDA meetings were held on April 24, 1997, October 9, 2001, and July 9, 2004.

Apotex submitted a Meeting Request/Background package dated November 16, 2004 for the purpose of discussing a proposal for the use of serum ferritin concentration as an endpoint in the measurement of chronic iron overload.

Discussion Points (bullet format):

Following introductions and introductory comments, the following questions/responses were discussed and agreed to. The firm's questions are provided in regular print, followed by the division's responses in bolded print.

Clinical questions

The ultimate goal of an iron chelator is to prevent and, if possible, to reverse iron-induced cardiac disease, which is responsible for most deaths in patients with chronic iron overload. There is now a considerable body of evidence that for patients with chronic iron overload, sequential serum ferritin concentrations are currently the most valuable prognostic indicator of disease progression, particularly for its most serious outcome, i.e., iron-induced cardiac damage.

Apotex submits that the most effective strategy for evaluating the efficacy of iron chelators should focus on their ability to prevent or reverse iron-induced cardiac damage. The briefing document in Section 6 Clinical Data Summary provides a background for discussing with the FDA the use of sequential assessments of serum ferritin concentration as the most important efficacy endpoint in clinical studies of Ferriprox, and the use of liver iron concentration and cardiac MRI assessments as secondary efficacy endpoints. Additionally, a differentiation is made between an estimate of total body iron load, which may be approximated by liver iron concentration, and the consequences of iron accumulation in the heart, manifested as heart disease. Finally, evidence is provided showing that serum ferritin concentration is not a surrogate marker for liver iron concentration, but serves as a prognostic indicator of iron-induced cardiac disease on its own.

Based on analysis of the value of currently available endpoints for assessment of the effectiveness of iron chelators, the efficacy data that will be submitted by Apotex in the NDA will be based primarily on sequential assessments of serum ferritin concentration and supported by liver iron concentration assessments, and cardiac MRI assessments.

1. Does the FDA agree that sequential measurements of serum ferritin concentration are an acceptable endpoint for assessing the efficacy of Ferriprox?

   - **No.**
   - **The majority of your studies that have investigated the clinical value of Deferiprone had as their primary endpoint an assessment of changes in tissue iron concentration, usually liver iron concentration. It is not appropriate to change the primary endpoint after these studies have been completed and the results are known.**
   - **The sponsor clarified that the intent of the question was not to change the clinical primary endpoint in the clinical studies (which are completed), but the sponsor is inquiring about using sequential measurements of serum ferritin concentration as an additional secondary endpoint.**
   - **The sponsor clarified that the analysis of serum ferritin measurements would be a meta analysis of the studies.**
   - **The Division responded that the analysis that the sponsor proposes may be useful. However, the review of the safety and efficacy of the studies will be based upon the**

protocol specified analysis. The decision on the application is based on the totality of evidence provided in the application.

- **We acknowledge the literature regarding sequential measurements of serum ferritin concentration and their proposed relationship to outcome, particularly in regard to morbidity and mortality from cardiac disease. However, the use of sequential measurement of serum ferritin as a surrogate marker of efficacy must be validated by demonstrating a clear relationship between prospectively targeted serum ferritin levels and morbidity and mortality in iron overloaded patients with β-thalassemia and other transfusion dependent anemias.**

- **In studies where sequential serum ferritin is used as an efficacy measure, patients should be followed long term to determine the correlation between sequential serum ferritin and clinical outcomes.**

- **We are willing to review any data that your studies provide that would indicate that sequential measurements of serum ferritin concentration are predictors of morbidity and mortality in iron overloaded patients with β-thalassemia and other transfusion dependent anemias and that modifying serum ferritin levels affect the clinical outcome.**

2. Does the FDA agree that the Apotex program for the clinical studies conducted for Ferriprox is appropriate to file for the intended claim:

   "Ferriprox is indicated for the treatment of chronic iron overload due to transfusion-dependent anemias. (b) (4) "

   - **Apotex may file intended claims that it believes are supported by the totality of the studies that it has conducted. The approved indication(s) will be based on a review of the data submitted. The data should be obtained from adequate and well controlled trials as indicated in the guidance for industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products".**

   - **The last two sentences of the intended claim do not seem appropriate for the Indications section of the package insert.**

   - **The firm agreed to delete the last two sentences.**

Regulatory questions

3. With the inclusion of additional Apotex-sponsored study LA-16 Randomized Trial comparing the relative efficacy of deferiprone in removing excess cardiac iron in thalassemia major patients and a Historical Controlled Study comparing the Apotex database for Ferriprox®

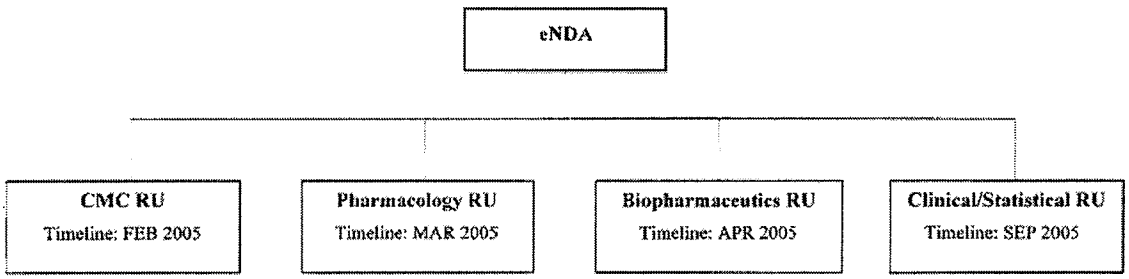
(deferiprone) against Desferal (deferoxamine) in support of the efficacy and safety for Ferriprox® (deferiprone), Apotex would appreciate feedback from the FDA on the timing and description of submission of portions of the NDA proposed by Apotex for the marketing approval of Ferriprox. A proposed schedule for submission of each portion of the NDA and a description of portions of the NDA are provided in Attachments 1 and 2, respectively.

- **The proposed schedule appears to be acceptable.**

Minutes Preparer: Alice Kacuba
Chair Concurrence: George Shashaty

Attachments

Attachment 1 **Proposed schedule for submission of each portion of the NDA**



Note: All reviewable units (RUs) will be accompanied by CTD Module 1

Attachment 2 Description of portions of the NDA

Reviewable Unit	Module	Content
CMC	1*	1.1 Forms 1.2 Cover letter 1.3 Administrative information 1.4 References section 1.5 Meetings 1.6 Other correspondence 1.7 Labeling
	2	2.1 CTD table of contents 2.2 CTD introduction 2.3 Quality overall summary
	3	Module 3 as per requirements in ICH guidance documents
Pharmacology	1*	Refer to Module 1 of the CMC RU
	2	2.1 CTD table of contents 2.2 CTD introduction 2.4 Nonclinical overview 2.6 Nonclinical written and tabulated summary
	4	Module 4 as per requirements in ICH guidance documents
Biopharmaceutics	1*	Refer to Module 1 of the CMC RU
	2	2.1 CTD table of contents 2.2 CTD introduction 2.5 Clinical overview 2.5.1 Product development rationale 2.5.2 Overview of biopharmaceutics 2.5.3 Overview of clinical pharmacology 2.5.7 Literature references 2.7 Clinical summary 2.7.1 Summary of biopharmaceutic studies and associated analytical methods 2.7.2 Summary of clinical pharmacology studies 2.7.5 References 2.7.6 Synopses of individual studies
	5	5.1 Table of contents for study reports and related information 5.2 Tabular listing of clinical studies 5.3 Clinical study reports 5.3.1 Reports of biopharmaceutic studies 5.3.3 Reports of human pharmacokinetic (PK) studies 5.4 Literature references

* All reviewable units (RUs) will be accompanied by CTD Module 1

Attachment 2 Description of portions of the NDA (Continued)

Reviewable Unit	Module	Content
Clinical/Statistical	1*	Refer to Module 1 of the CMC RU
	2	2.1 CTD table of contents 2.2 CTD introduction 2.5 Clinical overview 2.5.1 Product development rationale 2.5.4 Overview of efficacy 2.5.5 Overview of safety 2.5.6 Benefits and risks conclusions 2.5.7 Literature references 2.7 Clinical summary 2.7.3 Summary of clinical pharmacology studies 2.7.4 Summary of clinical safety 2.7.5 References 2.7.6 Synopses of individual studies
	5	5.1 Table of contents for study reports and related information 5.2 Tabular listing of all clinical studies 5.3 Clinical study reports and ISS ISE ISBR† Meta-analysis CRFs and CRTs 5.4 Literature references

* All reviewable units (RUs) will be accompanied by CTD Module 1
† ISBR will be included as part of the Module 2.5 Clinical Overview.

4 slides used by Sponsor during meeting

2. Does the FDA agree that the Apotex program for the clinical studies conducted for Ferriprox is appropriate to file for the intended claim:

"Ferriprox is indicated for the treatment of chronic iron overload due to transfusion-dependent anemias. (b) (4)

(b (b) (4)
((b) (4)

- **Apotex may file intended claims that it believes are supported by the totality of the studies that it has conducted. The approved indication(s) will be based on a review of the data submitted. The data should be obtained from adequate and well controlled trials as indicated in the guidance for industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products".**

- **The last two sentences of the intended claim do not seem appropriate for the Indications section of the package insert.**

Assessment of Tissue Iron Concentration

Study Code	N Enrolled (Duration)	LIC (SQUID/Biopsy)	Cardiac
LA01	• 35 Ferriprox • 36 DFO (2 +1 Year)	• 13 Ferriprox • 13 DFO (2 Year)	Available from pub. Literature (T2 in 54 pts)
LA16	• 29 Ferriprox • 32 DFO (1 Year)	• 27 Ferriprox • 29 DFO (1 Year)	•27 Ferriprox •29 DFO (T2* & Cardiac Function)
LA12	• 54 Ferriprox • 74 DFO (5 Years)	• 21 Ferriprox • 24 DFO (up to 5 Years)	Cardiac Disease & Survival (All Subjects)
Historical Control	•~300 (Up to 7 years)	Supportive	Cardiac Disease & Survival
LA03 (uncontrolled)	• 25 Ferriprox (up to 6 Years)	• 19 Ferriprox (up to 6 Years)	Available from pub. Literature (T2 in 23 pts)

Assessment of Tissue Iron Concentration

Study Code	N Enrolled (Duration)	LIC (SQUID/Biopsy)	Cardiac
LA01	• 35 Ferriprox • 36 DFO (2 +1 Year)	• 13 Ferriprox • 13 DFO (2 Year)	Available from pub Literature (T2 in 54 pts)
LA16	• 29 Ferriprox • 32 DFO (1 Year)	• 27 Ferriprox • 29 DFO (1 Year)	•27 Ferriprox •29 DFO (T2* & Cardiac Function)
LA12	• 54 Ferriprox • 74 DFO (5 Years)	• 21 Ferriprox • 24 DFO (up to 5 Years)	Cardiac Disease & Survival (All Subjects)
Historical Control	•~300 (Up to 7 years)	Supportive	Cardiac Disease & Survival
LA03 (uncontrolled)	• 25 Ferriprox (up to 6 Years)	• 19 Ferriprox (up to 6 Years)	Available from pub. Literature (T2 in 23 pts)

Does the FDA agree with the planned clinical content of the proposed NDA?

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

/s/

Alice Kacuba
1/6/05 05:03:37 PM

George Shashaty
1/6/05 05:48:08 PM

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

/s/

Alice Kacuba
7/3/2006 01:06:01 PM

Rafel Rieves
7/6/2006 12:01:48 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,724

Apotex Corporation
Attention: Marcie Macdonald (US Agent)
Associate Director, Regulatory Affairs
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

Dear Ms. Macdonald:

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

We also refer to the meeting between representatives of your firm and the FDA on July 9, 2004. The purpose of the meeting was as a pre-NDA meeting.

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) 827-9334.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
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 9, 2004
Time: 2:30-4 PM
Location: Parklawn Building, Chesapeake Conference Room

Application: IND 45,724; Ferriprox

Type of Meeting: Type B; Pre-NDA

Meeting Chair: Kathy Robie-Suh

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert L. Justice, M.D., M.S.; Division Director
Joyce Korvick, M.D.; Deputy Division Director
Kathy Robie-Suh, M.D., Ph.D.; Medical Team Leader, Hematology
George Shashaty, M.D.; Medical Reviewer
Jasti Choudary, B.V.Sc., Ph.D.; Supervisory Pharmacologist
Ramesh Raghavachari, Ph.D.; Chemistry Reviewer
Alice Kacuba, MSN, R.N., RAC; Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Stella Grosser, Ph.D.; Statistical Team Leader

Office of Information Service (HFD-142)

Zei-Pao Huang; Review Technology Staff

External Constituent Attendees and Titles:
Apotex

Fernando Tricta	V.P. Medical Affairs
Graziella Soulban	Clinical Director
John Connelly	Pre-clinical Director
Sonia Sanhueza	Director, Regulatory Affairs and Compliance
Tanya Konovalenko	Manager, Regulatory Affairs and Compliance
Elizabeth Gill	Manager, Clinical Data Management
Yu-chung Tsang	Director, Biopharmaceutics-Biostatistics

Background: On May 3, 2004, Apotex submitted a Meeting Request for a Pre-NDA meeting to discuss Ferriprox (deferiprone). A subsequent background package was submitted on June 7, 2004, which contained specific questions from the firm. Ferriprox is being investigated as an oral iron chelator. In preparation for today's meeting, the Division sent the firm, by facsimile, our initial responses. The bullets below were agreed to by both the Division and Apotex at the meeting. Apotex was given a copy of the responses at the conclusion of the meeting.

Discussion Points (bullet format):

Pre-clinical questions

1. The major elements of the preclinical program were determined in consultation with the FDA; does the agency agree that the scope of the current package (please see section 5) is sufficient to support approval of Ferriprox?

   - **The studies listed in section 5 alone are not sufficient. Please consult ICH Guidance "M3: Nonclinical Safety Studies for the Conduct of Human Trials for Pharmaceuticals, November, 1997". Your package should contain all types of studies described in the guidance document, e.g., additional genotoxicity and reproductive toxicity. Since you plan to administer the drug in a chronic fashion and since the drug is genotoxic, you will need to justify why carcinogenicity studies are not needed.**

2. Does the agency concur that the results of the recent preclinical studies (please see section 5) do not adversely affect the overall risk/benefit assessment for Ferriprox?

   - **We will need the full reports of the studies to answer this question. The assessment of risk/benefit depends on all data available, both clinical and preclinical, and the context of proposed use.**

3. Apotex is planning to provide individual animal data for all applicable pre-clinical studies in PDF format. Is this approach acceptable to the review division?

   - **PDF format for the studies and the individual data is acceptable. If during the course of review, data sets are needed for additional calculations, these should be provided in SAS transport files according to the 1999 guidance document.**

Clinical questions

4. Apotex would appreciate receiving feedback from FDA on the appropriateness of the Ferriprox drug development plan (please see Attachment 1) as part of the fast track program for the proposed indication.

- **The proposed studies appear to be appropriate but their adequacy is uncertain. Studies comparing deferiprone to Desferal are limited in terms of sample size and their power to detect differences in efficacy. The studies will be evaluated based on the safety and efficacy results.**

5. As part of the NDA submission, Apotex will be conducting a meta-analysis, as opposed to a "pooled" analysis, on the efficacy data obtained from clinical studies LA01, LA02/LA06 and LA03 (please see Table 14). Is this approach acceptable to the FDA?

   - **Please provide your definition of the terms "pooled analysis" and "meta-analysis" and indicate the differences between the two terms. The firm clarified that they would be doing a meta-analysis of individual patient data.**

   - **Meta-analyses are not used by the agency as the primary basis for approval. Adequate and well-controlled studies are needed to demonstrate efficacy and safety of the drug for its intended use. A meta-analysis could be presented in the ISE as additional support for the desired indication. The regulatory decision regarding approvability is made based on the totality of the evidence with regard to the benefits and risks.**

6. The FDA has requested submission of a historical comparison of both efficacy and safety databases. Since virtually all thalassemia patients in the developed world are prescribed deferoxamine, the only historical comparison in the last 20 years is based on patients treated with deferoxamine. As a follow-up to the FDA's request, Apotex proposes to provide the following:

   - Published literature on the outcome of patients treated exclusively with deferoxamine.
   - Safety data from the deferoxamine arm of clinical randomized trial of L1 and deferoxamine in thalassemia major (study LA-01, please see Attachment 2) and safety and efficacy of alternating deferoxamine (DFO) and deferiprone (L1) compared to DFO alone in the treatment of iron overload in thalassemia patients (study LA08-9702, please see Attachment 3).
   - Retrospective Assessment of Heart Failure and Survival During Iron Chelation with Deferiprone or Deferoxamine in Subjects with Transfusion-Dependent β-Thalassemia treated in a single treatment center (study LA12-9907, please see Attachment 4). Considering that the most serious outcome of transfusional iron overload is iron-induced cardiotoxicity and cardiac death, Apotex will provide comparative information on the incidence of cardiac disease and on the survival of patients treated for at least four years with Ferriprox or deferoxamine.
   - An epidemiological retrospective analysis of the survival in approximately 1000 patients treated with Ferriprox or deferoxamine in various treatment centers.
   - In addition, Apotex will request access to the following survival data of patients with Thalassemia:
     - The Cooley's Anemia Foundation database
     - The UK Thalassemia Register

Is this approach acceptable to the FDA?

- **The approach is acceptable.**

7. Ferriprox is being proposed for the treatment of chronic iron overload in patients with transfusion dependent anemias. The vast majority of patients participating in the Apotex-sponsored studies are patients with transfusion-dependent thalassemia, which we considered as the reference population for transfusional iron-overload. To further support the indication of Ferriprox for the treatment of chronic iron overload in patients with other transfusion dependent anemias such as patients with transfusion-dependent sickle cell disease or transfusion-dependent myelodysplastic syndromes, Apotex will submit the safety and efficacy data obtained on the compassionate use of Ferriprox for the treatment of patients with those conditions, and also the published literature on the use of deferiprone in patients with those conditions. Is this approach acceptable?

   - **The approach is acceptable. The efficacy and safety data will need to be sufficient to support the indication for each of the desired uses.**

8. Race was not collected for all clinical trials. In some cases we collected ethnicity and in some cases race and/or ethnicity. Using the draft "Guidance for Industry Collection of Race and Ethnicity in Clinical Trials" Jan 2003, we have mapped the ethnicity to the race classifications outlined in the OMB directive. Is this approach acceptable?

RACE / ETHNICITY COLLECTED	RACE CODE (MAPPING APPROACH)
AFRICAN	BLACK
BLACK	BLACK
CHINESE (JAMAICAN)	ASIAN
EAST INDIAN	ASIAN
GREEK/ITALIAN	WHITE
GUYANESE	ASIAN *
IRAQI	WHITE
PAKISTANI	ASIAN
TURKISH	WHITE
VIETNAMESE	ASIAN
CAUCASIAN	WHITE
CHINESE	ASIAN
LAOTIAN	ASIAN
ARABIC	WHITE
ASIAN	ASIAN
INDIAN	ASIAN
NA	NA
GREEK	WHITE
IRANIAN	WHITE

ITALIAN	WHITE

* based on additional information available to the sponsor

- **Yes, this is an acceptable approach.**

9. In the ISS, we have displayed the race categories descriptively. Given that Ferriprox is designated as an Orphan Drug, and that roughly 88% of subjects participating in the Apotex-sponsored studies would be classified as 'WHITE', is it necessary to perform additional analysis based on Race?

   - **Yes, you should perform analyses based on race in accordance with 21 CFR 314.50(d)(vi)(a).**

10. Most of the Apotex-sponsored studies were conducted prior to the implementation of MedDRA, and the adverse events during those studies were coded based on the COSTART dictionary. Adverse events for individual studies will be reported based on the COSTART dictionary. We have taken the initiative to remap the COSTART codes to MedDRA for the Integrated Safety Summary. Is this approach consistent with the FDA's current preference?

    - **Yes, it is acceptable. Please provide a data set comparing the verbatim term, the COSTART term to the MEDRA.**

11. The development program for Ferriprox, which was initiated in 1993, (b) (4) To address this issue, we propose to perform additional meta-analyses of the data for all patients (b) (4). Is this approach acceptable?

    - **The age range for which the drug is labeled will reflect the age range for which adequate data are available. Analyses of subsets of your exposed pediatric population would be useful in the NDA.**

Regulatory questions

12. Apotex would appreciate receiving feedback from the FDA on the structure, content, and timing of submission of portions of the application for marketing approval of Ferriprox. A proposed schedule for submission of each portion of the NDA and a description of portions of the NDA are provided in Attachments 5 and 6, respectively.

    - **The proposed schedule is acceptable.**

      Proposed schedule for the submission of each portion of the NDA:
      CMC Reviewable Unit: October 2004
      Pharmacology Reviewable Unit: December 2004
      Biopharmaceutics Reviewable Unit: January 2005
      Clinical Reviewable Unit: January 2005
      (Each Reviewable Unit will be accompanied by CTD Module 1)

- **See attachment for description of each Reviewable Unit.**

- **Please comply with the Guidance for Industry: Continuous Marketing Applications: Pilot 1-Reviewable Units for Fast Track Products Under PDUFA, June 2003.**

- **Manufacturing sites should be ready for inspections upon the submission of the first reviewable unit.**

- **Please clarify if you plan to submit a truly electronic CTD (eCTD) or a NDA in CTD format submitted in accordance with the 1999 guidance documents for electronic submissions (Regulatory Submissions in electronic Format: General Considerations and NDAs). If you plan to submit a truly electronic CTD (eCTD) in accordance with M2 eCTD: Electronic Common Technical Document Specification, April 2003, you will need to submit a sample for validation to the electronic document room (edr). This sample would need to be submitted prior to the submission of the first reviewable unit. If you are submitting a NDA in CTD format according to the 1999 guidance documents, please do not refer to the application as an "eCTD" or the edr will reject the submission upon receipt. Refer to the submission as a "NDA submitted according to the Guidance for Industry: Regulatory Submissions in Electronic Format". The firm clarified that they are not submitting a true eCTD. They are submitting an electronic NDA which contains some features of the CTD.**

13. In preparation of the Ferriprox submission in electronic format, Apotex has adopted the "shoe horn" approach described in the Providing Regulatory Submissions in Electronic Format – NDAs (1999) guidance document. As such, each folder in the electronic submission, named in accordance with the eNDA guidance document, contains a table of contents that corresponds to the CTD submission structure; Apotex would appreciate feedback on the proposed approach. A demo is provided in Attachment 7. Please refer to section 6 - Regulatory Summary for further clarifications and questions.

    - **It appears acceptable. However, please clarify why that there is a CRT folder placed outside the NDA 123456 folder. Generally, all data sets are put in the CRT folder under the submission folder. In this case, it should be under the NDA 123456 folder. The sponsor clarified that this was just for demo purposes.**

14. In accordance with 21 CFR 314.50(f)(1), the Case Report Tabulations section of the application contains tabulations of the data from each adequate and well-controlled study. It also states that routine submission of other patient data from uncontrolled or other studies is not required. Apotex plans to provide electronic CRTs, as per the current CDISC format (version 3.1), and as per the requirements stated above. Does the review division concur with this approach?

    - **You should provide Case Report Tabulations for all studies (controlled or uncontrolled) of deferiprone for the indication being sought.**

15. It is Apotex's understanding that if the company submits CRTs in the current CDISC format, then the review division may exempt submission of the patient profiles. Would the review division confirm that the CRTs submitted in this manner will be sufficient?

- **Patient profiles should be submitted for all patients who:**
  -Experienced serious adverse events
  -Withdrew from the study prematurely due to adverse events
  -Died

- **Case report forms for all deaths and withdrawal due to adverse events should be submitted. Additional information on CRFs may be requested during the course of the review.**

Minutes Preparer:

Chair Concurrence:

Attachment: Table as listed in the firm's June 7, 2004 Background Package for the content of each Reviewable Unit.

Description of portions of the NDA

Reviewable Unit	Module	Content
CMC	1*	1.1 Forms 1.2 Cover letter 1.3 Administrative information 1.4 References section 1.5 Meetings 1.6 Other correspondence 1.7 Labeling
	2	2.1 CTD table of contents 2.2 CTD introduction 2.3 Quality overall summary
	3	Module 3 as per requirements in ICH guidance documents
Pharmacology	1*	Refer to Module 1 of the CMC RU
	2	2.1 CTD table of contents 2.2 CTD introduction 2.4 Nonclinical overview 2.6 Nonclinical written and tabulated summary
	4	Module 4 as per requirements in ICH guidance documents
Biopharmaceutics	1*	Refer to Module 1 of the CMC RU
	2	2.1 CTD table of contents 2.2 CTD introduction 2.5 Clinical overview 2.5.1 Product development rationale 2.5.2 Overview of biopharmaceutics 2.5.3 Overview of clinical pharmacology 2.5.7 Literature references 2.7 Clinical summary 2.7.1 Summary of biopharmaceutic studies and associated analytical methods 2.7.2 Summary of clinical pharmacology studies 2.7.5 References 2.7.6 Synopses of individual studies

* All reviewable units (RUs) will be accompanied by CTD Module 1

	5	5.1 Table of contents for study reports and related information 5.2 Tabular listing of clinical studies 5.3 Clinical study reports 5.3.1 Reports of biopharmaceutic studies 5.3.3 Reports of human pharmacokinetic (PK) studies 5.4 Literature references

Proposed schedule for the submission of each portion of the NDA:
CMC Reviewable unit: October 2004
Pharmacology Reviewable unit: December 2004
Biopharmaceutics Reviewable Unit: January 2005
Clinical Reviewable Unit: January 2005

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

/s/

Alice Kacuba
7/27/04 12:14:39 PM

Kathy Robie-Suh
7/27/04 01:47:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,724

Apotex Corporation
Attention: Marcie Macdonald
Associate Director, Regulatory Affairs
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

Dear Ms. Macdonald:

Please refer to the teleconference between representatives of your firm and FDA on July 12, 2002.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, call me at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

DATE: July 12, 2002

APPLICATION NUMBER: IND 45,724; Ferriprox (deferiprone) Tablets

BETWEEN:

Name: Ms. Marcy Macdonald; Director of Regulatory Affairs, Apotex Corp. (US Agent)
Dr. Grahm Smith; Preclinical Expert, Apotex Inc.
Dr. Fernando Tricta; Medical Director, Apotex Inc.
Dr. Sonia Sanheuza; Director, Regulatory Affairs, Apotex Inc.

Phone: 847-573-9999
Representing: Apotex Corporation

AND

Name:
Dr. Joyce Korvick; Deputy Division Director
Dr. Kathy Robie-Suh; Medical Team Leader
Dr. Ruyi He; Medical Reviewer
Dr. Jasti Choudary; Supervisory Pharmacologist
Ms. Alice Kacuba; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

BACKGROUND:

IND 45,724; Ferriprox (deferiprone) Tablets is being investigated for the treatment of transfusion dependent iron overload. A Pre-NDA meeting was held on April 24, 1997, in which the need for the NDA to contain a complete preclinical data base with the full study reports was discussed (See meeting minutes dated June 18, 1997). A second pre-NDA meeting was held on October 9, 2001, in which the need for 12-month chronic toxicology studies was discussed (See meeting minutes dated October 29, 2001).

Subsequent to the October 9, 2001 meeting, on November 30, 2001, the firm submitted a request to waive the requirement for the [redacted] (b) (4) carcinogenicity studies. An Advice letter was issued on April 1, 2002 in which the Division denied that request.

The firm submitted a teleconference request on March 19, 2002 to further discuss this issue. On May 16, 2002, the firm submitted a list of topics to be discussed in the teleconference. The firm submitted a subsequent June 27, 2002 background package in preparation for the teleconference. A July 2, 2002 fax from the firm included a list of 6 specific questions to be addressed in the teleconference.

TODAY'S PHONE CALL:

Following introductions, the sponsor made an introduction which included the sponsor's view on the importance of the drug devlopement program for Ferriprox. Following this introduction, the sponsor's questions posed in the July 2, 2002 fax were discussed. The firm's questions are provided in regular print, followed by the division's responses in bolded print.

1. Apotex requests confirmation from the FDA that the following proposal provides the requested information for historical comparison of the efficacy and safety of deferiprone to that of deferoxamine.

   Apotex proposes to include in the NDA submission a combination of data generated by Apotex-sponsored studies and independent published studies, not funded by Apotex. The primary documentation in response to the FDA recommendation (See Apotex minutes form pre-NDA meeting dated October 22, 2001 and submitted to the FDA) will be a comparison of>100 patients treated with either deferiprone or deferoxamine (study LA-12; Appendix 1 background package). The study compares the incidence of cardiac disease, which is the main cause of death in thalassemia subjects, and the survival of patients treated with either therapy over the same period of time. In addition to the above study report, Apotex will also submit recent published literature, which we believe provides clear evidence of the benefits of deferiprone, particularly in comparison to that of deferoxamine, the only drug approved for marketing in the USA for the treatment of transfusional iron overload.

   - **The division reiterated the need for a proper historical control (patients with raw data). Historical control data can be from the same sites as the deferiprone data.**

   - **Published literature can be used to further support the adequate and well controlled study.**

   - **The Division discussed the need for inclusion of data from the patients not treated with deperiprone or deferoxamione. After a lengthy discussion, the firm decided that they will contact the Thalassemia Registry in the USA for information on patients not receiving treatment.**

2. Apotex requests FDA concurrence that the duration of the oral chronic toxicity studies be (b) (4) rather than 12 months as indicated in the FDA communication to Apotex dated April 1, 2002. To address the request, Apotex plans to initiate those studies in Q4, 2002. (b) (4) (b) (4)

   - (b) (4) (b) (4). **For a genotoxic drug intended for chronic use, the S4A ICH: Guidance on the Duration of Chronic Toxicity Testing in Animals (rodent and nonrodent toxicity testing) should be followed, which recommends 12-month studies.**

   - **The Division provided additional comments on the protocols in the background package:**

-On page 96 (protocol for Mouse Micronucleus Study), the study should employ animals of both sexes and the drug should be administered by the oral route.
-On page 97, the study in rats should be of 12 month duration and recovery animals in the high dose groups should also include non-iron loaded animals.
-On page 98, the study in monkeys should be of 1-year duration and recovery animals in the high dose groups should also include non-iron loaded animals.

3. Apotex expects to submit the NDA for Ferriprox by Q4 2002, thus Apotex respectfully requests from the FDA:

   -Acceptance of report of the mouse micronucleus study by Q1, 2003
   -Acceptance that reports for the (b) (4) studies will be provided to the FDA in Q4, 2003 and Q1, 2004, respectively. Apotex proposes to provide to the FDA with update reports following 6 months of deferiprone administration in rats and monkeys.

4. Apotex also requests that the NDA submission (Q4, 2002) and FDA review of the NDA (b) (4)

   Note: Question #3 and #4 were responded to together.

   - **This proposal would be developing the drug during the FDA review time and this is not in the spirit of FDAMA.**

   - **The Division reiterated the need for the full final study reports to be included in the NDA submission. This is based on: there is an approved drug for iron chelation; this drug will be used chronically; the clinical database is not going to be the traditional database. The published literature is not vast enough to obviate the need for the chronic toxicity studies. The preclinical toxicology data are needed in order to weigh the risk/benefit of the drug to humans.**

   - **The firm inquired about the possibly of submitting an interim analysis after 6 months. The Division stated that that would not be possible as the study reports would need to include histopathology data of all animals.**

5. Apotex would appreciate receiving guidance from the FDA regarding submission of the NDA under Section 505(b)(2).

   - **The efficacy data would need to include the raw data.**

6. The firm asked if they could contact Dr. Choudary for consult on the design of the preclinical studies.

- **The Division recommended that the most efficient way would be to submit the protocol for review and after the completion of the review, comments would be communicated in writing or by means of a teleconference.**

The call was then concluded.

Alice Kacuba
Regulatory Health Project Manager

Kathy Robie-Suh
Medical Team Leader

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

/s/

Alice Kacuba
8/23/02 10:43:10 AM

Kathy Robie-Suh
8/23/02 05:08:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,724

Apotex Corporation
Attention: Marcie Macdonald (US Agent)
Associate Director, Regulatory Affairs
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

Dear Ms. Macdonald:

Please refer to the cmc pre-NDA meeting between representatives of your firm and FDA on October 10, 2001.

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) 827-1602.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 10, 2001
Time: 11:30 – 1 PM
Location: Parklawn Building, Conference Room "C"

Application: IND 45,724, Ferriprox (deferiprone) Tablets

Type of Meeting: Type B/Pre-NDA CMC meeting

Meeting Chair: Liang Zhou

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Liang Zhou, Ph.D; Chemistry Team Leader
Maria Ysern; Chemistry Reviewer
Alice Kacuba; Regulatory Health Project Manager

Division of New Drug Chemistry II (HFD-820)

Eric Duffy, Ph.D.; Division Director

External Constituent Attendees and Titles:

David Coffin-Beach, BS.Pharm, Ph.D.; President, Torpharm
Marcy Macdonald; Associate Director, RA, Apotex Corp. U.S.A. (U.S. Agent)
Sonia E. Sanhueza, Ph.D.; Director, Regulatory Affairs and Compliance
(b) (4)
(b) (4)
Elisabeth Kovacs; Senior Director Pharmaceutical Research
Stephen Horne, Ph.D.; Director of Manufacturing Development, Brantford Chemicals, Inc.

Background: IND 45,724 for Ferriprox (deferiprone) Tablets is being investigated for use as an iron chelator. On July 25, 2001, Apotex requested a Pre-NDA meeting to discuss the submission of an NDA for deferiprone. On September 4, 2001, Apotex submitted a background package (BGP). On September 10, 2001, Apotex submitted revised questions for the Agency to address. A separate clinical Pre-NDA meeting was held October 9, 2001.

The format of these minutes provides for the sponsor's questions in regular print followed by the Agency's responses in bolded print.

Discussion Points (bullet format):

At the beginning of the meeting, handouts, which included the sponsor's revised questions with the Agency's responses, were distributed to all meeting attendees.

The sponsor presented brief presentation. Copies of the slides were distributed to the meeting attendees. See the October 18, 2001 submission for a copy of the slides used during the sponsor's presentation.

1. Would FDA be prepared to receive and review an NDA either entirely in the CTD format or where just the CMC section is presented in the CTD format?

   - **It would be acceptable to present the CMC section in the CTD format.**

2. Apotex would like FDA feedback on the adequacy of the stability protocols, with emphasis on the conditions and lots studied (CMC Pre-NDA package Vol. 1, Appendices 1 and 2).

   - **It appears to be acceptable. The HPLC Assay method should be stability indicating. Representative chromatograms should be submitted to the NDA.**

   - **Please follow the ICH Q1A and Q1B Guidelines.**

3. Apotex would like feedback from the FDA on the results provided in Vol. 1, Appendices 1 and 2 to support the retest dating of (b) (4) months for the drug substance and expiration date of (b) (4) for the drug product. We understand that FDFA cannot officially approve dating in the absence of the complete NDA and a full statistical analysis on the data?

   - **It is premature to discuss this. This is a NDA review issue.**

4. Apotex would like feedback on the appropriateness of the drug substance and drug product specifications based on the data presented in Vol. 1, Appendix 3, Batch Histories. Does FDA feel the specifications are supported by the appropriate data?

   - **The final specifications will be based on data obtained from lots used to demonstrate manufacturing consistency and are chosen to confirm the quality rather than characterize the product. (Refer to ICH Q6A).**

   - **T (b) (4) and the loss on drying specifications seem broad.**

   - **The (b) (4) also seems too broad although below USP requirements.**

   - **The proposed specifications for related compounds in DP seem wide.**

- **Follow ICH Guidelines Q3A, Q3B for reporting impurities, degradation products, etc.**

5. Apotex asks FDA to further explain the request for conduct of dissolution studies at a variety of PHs (Vol. 1). The conversations resulting in this request were held in 1997 and Apotex would like to ensure they perform studies that FDA will find acceptable today.

   - **Ideally the conditions employed in the dissolution method should not release the drug too rapidly or too slowly and should be able to discriminate any batch to batch variations. Dissolution data obtained at different pHs (1.0, 4.5, 6.8, and 7.4) may allow the selection of the most appropriate pH for that particular product.**

   - **For Ferriprox, (b) (4) of deferiprone dissolved in 45 minutes suggests that the method may be adequate pending detailed review of the data by the Agency (detailed methodology information is unavailable from the meeting package). However, the Agency would still prefer that you submit dissolution data at various pHs.**

Additional CMC Comments:

- **No USAN name is provided.**

- **As part of the NDA review, upon submission of the NDA, a consult for tradename review will be sent to OPDRA. You may request an OPDRA tradename review during the IND stage. However, products with user fee dates have priority. If you choose to request an OPDRA tradename review during the IND stage, the request should be in writing and the IND amendment should include a copy of the proposed package insert, bottle label, and carton label. If the OPDRA tradename review is requested and completed during the IND stage, it will need to be re-evaluated again during the NDA review cycle.**

- **An HPLC method, (combined with the UV test), would be recommended as an Identity test.**

- **With regard to the starting materials please consider the following:**

  -The DMF holders should be notified that for the starting materials it is necessary to provide a list of the sources, Certificates of Analysis, and if necessary, references describing the synthetic process.

  -Acceptance specifications should be provided.
  -A change protocol to describe how the starting material will be qualified when a new vendor is considered or significant changes are done to the synthetic process (i.e., well defined impurity profile, analytical methods used to identify impurities,

provisions to reassess the adequacy of the existing impurity methods to insure that new or potential synthetic impurities will be adequately controlled, provisions to augment the acceptance specifications for the starting materials with vendor specific attributes).

- **The summary volume of the NDA should contain a definitive statement that all manufacturing facilities are ready for inspection at the time of the NDA submission.**

- **The summary volume of the NDA should contain a table which includes: all of the manufacturing facilities, complete address, contact name and number, function(s) of each facility, and the CFN number for each facility.**

Minutes Preparer:

Chair Concurrence:

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

/s/

Alice Kacuba
10/26/01 03:15:14 PM

Liang Zhou
10/26/01 04:35:38 PM

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

/s/

Alice Kacuba
10/28/01 01:25:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,724

Apotex Corporation
Attention: Marcie Macdonald
Associate Director, Regulatory Affairs
50 Lakeview Parkway
Suite 127
Vernon Hills, IL 60061

Dear Ms. Macdonald:

Please refer to the clinical pre-NDA meeting between representatives of your firm and FDA on October 9, 2001.

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) 827-1602.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 9, 2001
Time: 2:00 – 3:30 PM
Location: Parklawn Building, Conference Room "C"

Application: IND 45,724, Ferriprox (deferiprone) Tablets

Type of Meeting: Type B/Pre-NDA meeting

Meeting Chair: Victor Raczkowski

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczkowski, M.D., M.Sc.; Acting Director
Joyce Korvick, M.D.; Deputy Director
Kathy Robie-Suh, M.D., Ph.D.; Medical Hemotology Team Leader
Ann Farrell, M.D.; Medical Reviewer
Ruyi He, M.D.; Medical Reviewer
Min Lu, M.D.; Medical Reviewer
Edvardas Kaminskas, M.D.; Medical Reviewer
Jasti Choudary, B.V.Sc., Ph.D.; Supervisory Pharmacologist
Alice Kacuba, R.N., MSN, RAC; Regulatory Health Project Manager
Liang Zhou, Ph.D; Chemistry Team Leader

Division of Pharmaceutical Evaluation II (HFD-870)

Suliman Al-Fayoumi, Ph.D.; Biopharmaceutics Reviewer

Division of Biometrics II (HFD-715)

Tom Permutt, Ph.D.; Statistics Team Leader

Office of Orphan Product Development (HF-35)

Jeff Fritsch, Project Manager

External Constituent Attendees and Titles:

Marcy Macdonald; Associate Director, RA, Apotex Corp. U.S.A. (U.S. Agent)
Sonia E. Sanhueza, Ph.D.; Director, Regulatory Affairs and Compliance
Graham Smith, Ph.D.; Pre-Clinical Director
Michael Spino, Pharm.D.; Senior Vice-President, Scientific Affairs

Fernando Tricta, M.D.; Medical Director
Yu-Chung Tsang, Ph.D.; Manager, Pharmacokinetics

(b) (4)

[redacted]

Background: IND 45,724 for Ferriprox (deferiprone) Tablets is being investigated for the use as an iron chelator. On July 25, 2001, Apotex requested a Pre-NDA meeting to discuss the submission of an NDA for deferiprone. Apotex submitted a background package (BGP) on September 4, 2001. On September 10, 2001, Apotex submitted revised questions for the Agency to address. A separate CMC Pre-NDA meeting is scheduled for October 10, 2001.

The format of these minutes provides for the sponsor's questions in regular print followed by the Agency's responses in bolded print.

Discussion Points (bullet format):

- At the beginning of the meeting, handouts, which included the sponsor's revised questions with the Agency's responses, were distributed to all meeting attendees.

- The sponsor presented a 10 minute presentation on the development of Ferriprox. See the sponsor's October 18, 2001 submission for a copy of the slide presentation.

1. Based on the review of the safety data as presented in the Draft Overall Safety Report (Pre-NDA package of the Pre-clinical and clinical information, Vol. 5) does FDA agree with Apotex that safety issues have been addressed sufficiently to file the NDA with this data cutoff of February 25, 2001?

    - **The safety data appear to be sufficient to file the application. However, the adequacy of the safety data for product approval is a review issue.**

    - **We have some safety concerns (e.g., neutropenia or agranulocytosis) that need to be addressed in the NDA. Each case of neutropenia or agranulocytosis should be fully detailed and should also be described completely in narrative form. The integrated summary of safety (ISS) should contain specific sections that address these events.**

    - **We note a high rate of patient withdrawals. Each case will need to be presented fully and explained. Withdrawals should be analyzed with an appropriate comparator for safety. This could be accomplished by a historical control.**

(b) (4)

[redacted]

(b) (4)

(b) (4) Use of concurrent controls should also be explored and do not preclude evaluation using historical controls. Use of both approaches should be considered.

- **In the NDA, provide an explanation for why some studies were terminated early.**
- **All foreign postmarking experience data should also be submitted in the NDA.**
- **The safety database for the NDA should be as complete as possible. The cutoff date proposed for your submission is more than 7 months prior to the submission. We recommend a later cutoff date.**

2. Apotex has filed regulatory submissions with EMEA and other countries and received their approval for marketing. In what manner would FDA like the clinical safety and protocol data to be submitted to FDA in the NDA for consideration of US approval?

   - **Please meet all of the regulatory requirements of 21 CFR 314.50.**
   - **Please describe what was submitted to the other countries, focusing on areas in which the content or format of the application differ from what FDA typically receives.**

3. Most of the patients participating in the Apotex trials had thalassemia major but there are other iron overload conditions (b) (4) in which the use of Ferriprox could be beneficial. Because of the very limited number of patients in the USA (estimated to be less than 200) no clinical studies have been conducted in patients with these conditions. Do the available data as presented in Vol. 4 and 5 suffice for the use of Ferriprox as a second line therapy also for these patients?

   - **Labeling is a review issue. However, in the application, include the data on all patients who have received Ferriprox for any disease.**
   - **Support for these indications does not appear to be strong. However, if you wish to have the conditions** (b) (4) **considered as part of the NDA, please clearly distinguish safety or efficacy data in patients with these conditions from the data of patients with thalassemia major. Also, in the NDA, provide a complete justification of why such conditions should be considered for approval and highlight any safety issues that you would expect to see in these conditions.**

4. Apotex would appreciate the identification of the statistician assigned to review the NDA upon submission.

- **The specific statistical reviewer will be assigned upon submission of the NDA.**
- **In the meantime, contact people would be Alice Kacuba (RHPM) and Tom Permutt (Statistical Team Leader).**

5. Deferiprone was not developed following the traditional US preclinical guidelines. However, Apotex believes sufficient preclinical data exist to adequately characterize human risk. (b) (4) Does FDA agree?

   - **We disagree. At a minimum, you will need to conduct valid 1-year chronic toxicity studies in rodent and non-rodent species.**
   - **Considering the genotoxic nature of the drug and the proposed chronic indication, carcinogenicity studies in rats and mice are also desirable.**
   - **These studies should be conducted with both iron-overloaded and normal animals.**

   It was the sponsor's position that because they now have more clinical data than in 1997, the clinical data superceded the need for the chronic toxicity studies. The sponsor asked whether it would be sufficient to conduct chronic toxicity studies of (b) (4) duration in non-rodent species. The Division indicated that for a genotoxic drug without carcinogenicity studies and intended chronic use, chronic toxicity studies of one year duration are needed. The Division asked the sponsor to submit their proposals for further consideration.

6. Apotex believes the clinical program conducted under US/IND, in addition to the data submitted to the EMEA and other countries from whom marketing approval has been granted (as outlined in the Apotex pre-NDA submission Volumes 4 and 5) is sufficient to support product approval in the US. Does the Agency agree?

   - **Approval of an application is data dependent and is a review issue. A decision on approval can be made only after a comprehensive review of the entire application has been completed.**
   - **The current efficacy database, as presented in the background package, does not appear to be strong.**
   - **Provide a clear presentation of the safety and efficacy of Ferriprox. Particularly, present comparisons between groups of safety and efficacy data for all controlled studies. If what has been included in the background package represents all the available data, submit a historical comparison of the efficacy database. Also submit a historical comparison of the safety data.**

7. Apotex would appreciate receiving feedback from FDA on the responses (Vol. 4) to the following FDA questions raised at the previous meeting in 1997:

"...the clinical database, as presented does not satisfy the regulatory requirements for adequate and well-controlled studies...an adjudication committee could re-evaluate the safety and efficacy data compared to an historical control in a similar patient population."

- **This is still our position.**

"...Efficacy endpoints must be linked to a clinical improvement, such as slowing of disease progression."

- **Include in the NDA, a discussion of endpoints in relation to disease progression.**

"...Serum ferritin must be a validated surrogate for hepatic iron concentration (HIC)."

- **During the review of the application, for efficacy, we will be looking for consistency of drug effect across the measured variables.**

- **These are all review issues.**

Additional comments

- **Provide an estimated time of NDA submission.**

  The sponsor stated that the estimated time of NDA submission would be approximately July 2002.

- **The NDA should contain all of the needed requirements for Section 6 of the NDA.**

Minutes Preparer:

Chair Concurrence:

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

/s/

Alice Kacuba
10/29/01 04:11:24 PM

Victor Raczkowski
10/29/01 04:40:18 PM

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

/s/

Alice Kacuba
10/29/01 05:25:51 PM