Akebia Therapeutics
245 First Street, Suite 1400
Cambridge, MA 02142

617.871.2098
Akebia.com

13 March 2020

Norman L. Stockbridge MD, PhD
Division Director
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
Attn: Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RESPONSE TO PREA NON-COMPLIANCE LETTER
DEFERRAL EXTENSION REQUESTED

Re: New Drug Application (NDA) 205874: Auryxia® (ferric citrate) Tablets
(eCTD Sequence No. 0166)

Dear Dr. Stockbridge,

Reference is made to Keryx Biopharmaceuticals, Inc.'s (Keryx) New Drug Application (NDA) 205874 for Auryxia® (ferric citrate) tablets approved on 5 September 2014 for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis. Reference is also made to Keryx's Investigational New Drug (IND) 052868 for the development of ferric citrate with specific reference to Sequences 0107, 0115, 0137, and 0138 (18 Sept 2018 Final Pediatric Study Protocol [redacted] (b) (4)

This submission includes our formal response to the **Pediatric Research Equity Act (PREA) Non-Compliance Letter** dated 31 January 2020, which includes a Request for Deferral Extension. Please be advised that Keryx and Akebia Therapeutics, Inc. (Akebia) merged on 12 December 2018, with Keryx becoming a wholly owned subsidiary of Akebia (the Merger). Summarized below are the communications between Keryx and the Division regarding the proposed pediatric protocol followed by an explanation of our request for a Deferral Extension. Please accept our sincere apologies for our failure to meet our PREA commitments within the required time frame.

Background

The NDA approval letter for Auryxia stipulates a deferred Post Marketing Requirement (PMR) under PREA (PMR 2104-1). The original timeline for pediatric assessment that FDA included in the NDA Approval Letter is provided below.

2104-1 A multi-center clinical trial to evaluate the dosing and safety of ferric citrate for the treatment of hyperphosphatemia in children ages six months to < 18 years with chronic kidney disease.

Final Protocol Submission: 8/31/15
Study Completion: 6/30/19
Final Report Submission: 12/31/19

Follow approval of the NDA, however, Keryx had additional interactions with the Division of Cardiovascular and Renal Products (the Division) regarding the overall pediatric development plan for Auryxia. As reflected in the chronology below, Keryx submitted a Proposed Pediatric Study Request (PPSR) prior to approval of the original NDA and continued to discuss the pediatric study program with the Division until early this year. In May 2015, FDA issued a Pediatric Written Request (PWR) under the Best Pharmaceuticals for Children Act (BPCA) for Study (b) (4) which is the same study that FDA required under PREA. These communications demonstrate Keryx's continued commitment to conduct a pediatric study program for Auryxia and to fulfill the PMR in the original approval letter. The key communications between Keryx and the Division are listed below for the Division's reference.

Date	Keryx/FDA Communication	Type of Submission/Comments
25 July 2013	Keryx	Seq 0107, IND 52868 - Proposed Pediatric Study Request (PPSR) Submission
27 February 2014	FDA	Inadequate Study Request
18 March 2014	Keryx	Seq 0115, IND 52868 - Revised PPSR Submission
05 September 2014	FDA	Initial NDA 205874 Approval
29 May 2015	FDA	FDA issued (PWR)
11 January 2016	Keryx	Information Request- Nonclinical Rat Juvenile Toxicology Protocol
03 March 2016	FDA	FDA Advice- Feedback on Nonclinical Rat Juvenile Toxicology Protocol
07 April 2017	Keryx	Type C Meeting Request to amend PWR
14 June 2017	FDA	Type C Preliminary Comments
27 September 2017	FDA	Advice/Information Request – FDA Request for an Additional Definitive Juvenile Rat Toxicology Study
02 February 2018	Keryx	Seq 0137, IND 52868 Draft Pediatric Clinical Protocol ((b) (4)
04 June 2018	FDA	FDA Advice- Feedback on the Draft Pediatric Clinical Protocol ((b) (4)
18 June 2018	FDA and Keryx Teleconference	No official Meeting Minutes from FDA. Keryx Meeting Minutes: • FDA agreed to modify the protocol to restrict enrollment of subjects from (b) (4) who can be dosed with current available formulation. • Enrollment of children (b) (4) years is further subject to acceptable results in an additional juvenile rat toxicity study.
20 September 2018	Keryx	Seq 0138, IND 52868- Final Pediatric Protocol ((b) (4)
22 January 2020	FDA	Project Manager sent an email to Keryx recommending modification of the Pediatric Protocol ((b) (4) doses

Request for Deferral Extension

Akebia submits this Request for Deferral Extension on behalf of Keryx. Akebia acknowledges, and deeply regrets, the delay in the pediatric development of Auryxia, which was due in large part to significant unanticipated developments, including: 1) the Merger, 2) the loss of key experts including regulatory staff and clinical staff following the Merger, and 3) evolving thinking for the pediatric development program for the product, as discussed with FDA over the past several years. After on-boarding new regulatory and clinical staff, the new team reviewed all historical information and held a Pediatric Advisory Board meeting with key medical experts in pediatric nephrology in December of 2019 to better understand the opportunities and challenges of pediatric study execution and best practices. Following this Advisory Board meeting, the Akebia team conducted a feasibility assessment to determine the probable rate of patient population recruitment. Akebia then updated the pediatric protocol with the recommended doses and plans to submit the Pediatric Protocol Amendment to the IND 052868 (b) (4).

Akebia requests a Deferral Extension with the proposed dates set forth below. This timeline takes into consideration: 1) the previous work we have done on the Protocol Amendment, allowing us to submit the Amended Protocol with the FDA-recommended doses promptly; 2) the time we believe it will take to activate study sites; and 3) predicted pediatric population recruitment rates (estimated to be (b) (4) patients per site per month). Akebia intends to try to expedite recruitment and will keep the Division informed of its recruitment activities.

Akebia is committed to fulfilling our PREA requirements with diligence. We hereby request for a Deferral Extension with the following timeline for PMR 2104-1:

Final Protocol Submission: 03/16/2020
Study Completion: 12/01/2025
Final Report Submission: 06/01/2026

If you have any questions or comments regarding this submission, please do not hesitate to contact me. Thank you for your understanding and consideration.

Sincerely,

Molly E Shea

Molly E Shea, PhD
Vice President, Regulatory Affairs
Akebia Therapeutics, Inc.
245 First Street, Suite 1400
Cambridge, MA 02142
Telephone: 857-777-6584; Fax: 617-871-2089
Email: mshea@akebia.com

U.S. FOOD & DRUG
ADMINISTRATION

NDA 205874

NOTIFICATION OF NON-COMPLIANCE WITH PREA

Akebia Therapeutics
Attention: Carly Evans
Senior Director, Regulatory Affairs CMC and Operations
245 First Street, Suite 1400
Cambridge, MA 02142

Dear Ms. Evans:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Auryxia (ferric citrate) Tablets, which was approved on September 5, 2014.

The Agency has determined that you have failed to meet the postmarketing requirement (PMR) of the Pediatric Research Equity Act (PREA) for this application because you have not yet submitted your pediatric assessment for PMR 3153-1, which was deferred until December 31, 2019. Therefore, we are hereby notifying you that due to your failure to submit either a pediatric assessment or a request for a deferral extension, you are not in compliance with federal law.

Under the provisions of section 505B(d)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 355c(d)(1)], you must respond in writing within 45 calendar days of the date of this letter. Your response should include the reason(s) for the delayed pediatric assessment and a date by which you expect to submit the assessment. You may also include a request for a deferral extension, if applicable, which should be identified as a "**DEFERRAL EXTENSION REQUESTED**" in your response.

In accordance with the FD&C Act, FDA will post this letter and your response to the website at https://www.fda.gov/drugs/development-resources/non-compliance-letters-under-505bd1-federal-food-drug-and-cosmetic-act with redactions for any trade secrets and confidential commercial information 60 calendar days from the date of this letter.

Please identify your response to this letter as a "**RESPONSE TO PREA NON-COMPLIANCE LETTER.**" To facilitate our review, submit this information to your NDA with a cross-reference letter to the Investigational New Drug Application (IND) to which your protocol has been submitted.

If you have any questions, call Sabry Soukehal, Regulatory Project Manager, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
01/31/2020 03:08:04 PM

Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

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Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	14.2.4814.1101
Virus Definition Date	03/12/2020 rev. 20
Submission Size	Approx. 3.3 MB

The Primary IT point of contact for this submission is:

Name	Molly Shea
Phone Number	(857) 777-6584;
Email Address	mshea@akebia.com