CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215192Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 102465

MEETING MINUTES

Akebia Therapeutics, Inc.
Attention: Debleena Sengupta, PhD, RAC
245 First Street, Suite 1400
Cambridge, MA 02142

Dear Dr. Sengupta:

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

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2020. The purpose of the meeting was to discuss the proposed content of the planned NDA and overview of the data from the global phase 3 studies.

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

If you have any questions, call Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, ACNP-BC
Clinical Team Leader
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 29, 2020, 8 – 9 AM (ET)
Meeting Location: Teleconference

Application Number: IND 102465
Product Name: vadadustat
Indication: treatment of anemia associated with chronic kidney disease
Sponsor Name: Akebia Therapeutics, Inc.
Regulatory Pathway: 505(b)(1)of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Virginia Kwitkowski, MS, ACNP-BC
Meeting Recorder: Carleveva Thompson, MS

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Ellis Unger, MD, Director

OCHEN, Division of Nonmalignant Hematology (DNH)
Albert Deisseroth, MD, PhD, Supervisory Associate Director
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader
Fadi Nossair, MD, Clinical Reviewer

OCHEN, Division of Pharm/Tox (DPT)
Todd Bourcier, PhD, Nonclinical Team Lead (Acting)
Pedro Del Valle, PhD, Nonclinical Reviewer
Bo Yeon Lee, PhD, Nonclinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Lead
Sarabdeep Singh, PhD, Statistical Reviewer

Office of Pharmaceutical Quality (OPQ)
Liya Tang, PhD, CMC Reviewer
Steve Rhieu, PhD, CMC Reviewer

Office of Regulatory Operations (ORO)
Carleveva Thompson, MS, Regulatory Project Manager

SPONSOR ATTENDEES

Akebia Therapeutics, Inc.
Steven Burke, Sr. Vice President, Research & Development and Chief Medical Officer
Geoff Ross, Sr. Vice President, Clinical Development, Drug Safety, Pharmacovigilance, and Medical Affairs
Dennis Vargo, Vice President, Drug Safety and Pharmacovigilance
Youssef Farag, Director, Medical
Mike Collins, Sr. Vice President, Clinical Operations and Data Sciences
Wenli Luo, Sr. Director, Biostatistics
Molly E. Shea, Vice President, Regulatory Affairs
Debleena Sengupta, Director Regulatory Affairs

Otsuka
Bob McQuade, Executive Vice President, Chief Strategic Officer
Charlotte Jones-Burton, Vice President, Global Clinical Development, Nephrology
Michael Fahmy, Sr. Director, Global Regulatory Affairs
Catherine Sheppard, Director, Global Regulatory Affairs

1.0 BACKGROUND

Vadadustat is a synthetic, orally bioavailable, small molecule that inhibits hypoxia-inducible factor (HIF) prolyl-hydroxylase (PH) enzymes, leading to stabilization and increased levels of hypoxia inducible-factor alpha, resulting in stimulation of erythropoietin (EPO) expression and improved production of Hb and red blood cells (RBCs). Based on the proposed mechanism of action, a research and development program was opened under IND 102465 in 2009 and trials were conducted to characterize the safety and efficacy of oral vadadustat tablets to treat anemia associated with chronic kidney disease (CKD), in patients on and not on dialysis. There have been 20 completed phase 1 studies (including 1 regional Japanese study), 8 completed phase 2 studies (including 2 regional Japanese studies), and 8 completed phase 3 studies (4 pivotal global phase 3 and 4 supportive regional Japanese phase 3 studies). There are 2 ongoing/planned phase 3b studies that evaluate different vadadustat dosing regimen in patients on dialysis.

Vadadustat has been studied for the treatment of anemia associated with CKD including in 4 global phase 3 studies. The global phase 3 studies include two studies in adult subjects with anemia associated with NDD-CKD (PRO2TECT Studies: AKB-6548-CI-0014 and AKB-6548-CI-0015) and 2 studies in adult subjects with anemia associated with DD-CKD (INNO2VATE Studies: AKB-6548-CI-0016 and AKB-6548-CI-0017). All 4 studies were multi-center/multi-nationals, randomized, open-label, sponsor-blinded, active-controlled (darbepoetin alfa), non-inferiority efficacy and safety CV outcome studies. The primary endpoint for efficacy was mean change in Hb between Baseline and Weeks 24 to 36. The primary safety endpoint assessed major adverse cardiovascular event (MACE) parameters (defined as death, non-fatal MI and non-fatal stroke), specifically as time to first MACE, which was used in sample size determination

for each of the programs. Each study had a vadadustat starting dose of 300 mg once-daily with the opportunity to dose titrate from 150 to 600 mg once-daily to reach and maintain Hb at the targeted range (10-11 g/dL in US and 10-12 g/dL Ex-US). The Hb target ranges for US and Ex-US were established based on FDA and European Medicines Agency's (EMA's) guidance to follow Hb targets established in the US Prescribing Information (PI) and Summary of Product Characteristics (SmPC) for ESAs, respectively. Study duration was 36 weeks, with the opportunity to continue on long-term treatment until trial completion.

The purpose of the meeting is to provide a preview of the proposed structure and content of the planned NDA in advance of the NDA submission and an overview of the data from the global phase 3 studies. The expected outcomes of the meeting are to:

- Reach agreement that the global phase 3 studies are sufficient to support NDA Filing for the target indication in the US
- Reach agreement on a select topic for CMC for the planned NDA
- Review and reach agreement on the structure and content of the planned NDA
- Reach agreement that the clinical pharmacology program supports NDA filing
- Reach agreement that a Pregnancy Exposure Registry is not required
- Reach agreement on the proposed dates and content for the 120-day safety update
- Align on Akebia's approach for regulatory administrative information inclusion in the NDA

FDA sent Preliminary Comments to Akebia Therapeutics on October 20, 2020.

2.0 DISCUSSION

FDA Preamble: To evaluate the risk of cardiovascular AEs associated with vadadustat administration, a safety endpoint was defined for both the PRO2TECT program and the INNO2VATE program, as time to first MACE. Akebia powered its pivotal trial programs, in relation to both duration of treatment and sample size, to reach sufficient number of MACE per program, which was deemed adequate to provide statistical support to any non-inferiority conclusions resulting from the pivotal trials. In addition, there was agreement that successful demonstration of non-inferiority, in relation to active comparator (i.e. darbepoetin alfa), on both primary efficacy and primary safety endpoints will be necessary for approval for the proposed specific indication. As per summary efficacy results provided in the meeting package, you demonstrated non-inferiority for efficacy for patients with anemia associated with CKD, who were on dialysis and not on dialysis via Hemoglobin (Hb) endpoint. In addition, you demonstrated non-inferiority for the safety MACE endpoint for patients with anemia associated with CKD, who were on dialysis. However, the MACE analysis conducted in the 'not on dialysis' population did not demonstrate non-inferiority to darbepoetin.
We acknowledge you provided a summary of subgroup analysis results on the MACE endpoint for different regions, including US vs. Ex-US for the MACE primary

and other key secondary endpoints. However, they are post-hoc findings. Due to concerns relating to insufficient power associated with subgroup sample size and inherent bias associated with multiplicity analyses without the presence of any mitigating strategy, we consider these results exploratory and hypothesis-generating in nature.

Whether you have demonstrated adequate evidence for the safety of vadadustat will ultimately be a review issue. To further evaluate the consistency across the studies and ensure the robustness of the results, in addition to analyses you conducted based on the pooled study data, please conduct key analyses for individual studies based on the intent-to-treat (ITT) population and Per-Protocol (PP) population regardless of whether the patient was on or off study treatment. Also, provide meta-analysis results by combining the estimates of hazard ratio (HR) from the Cox model of individual studies, and weights inversely proportional to the variance of the trial-specific log HR estimates to obtain an overall treatment effect.

Meeting Discussion: The Agency agrees that not all subgroup analysis detailed in the briefing package provided were post-hoc in nature. Specifically, the following analyses were pre-specified:

1) **Subgroup analysis of MACE endpoint by region (US, Europe, and ROW), specifically looking at HR and proportion of subjects with primary safety endpoint per arm for US vs. Ex-US (i.e., Europe & ROW) vs. global.**

2) **Subgroup analysis of MACE endpoint by age group, specifically looking at HR of subjects with primary safety endpoint for <65 years vs. >65 years, by region (i.e., US vs. Ex-US vs. global).**

However, the following analyses proposed in the briefing package were post-hoc in nature, as indicated by the Sponsor and when compared to the SAP:

1) **Subgroup analysis of MACE endpoint by age as a continuous variable, specifically looking at HR of subjects with primary safety endpoint for age.**

2) **Subgroup analysis of 3 endpoints of primary MACE, expanded MACE, and all-cause mortality by PEP Hb level in Ex-US subjects only, specifically looking at associated HR for Hb ≤11 g/dL vs. Hb >11 g/dL.**

3) **INNO2VATE and PRO2TECT combined: MACE tables/figures for global population and by region (US, Europe, ROW, Ex-US).**

Even though the SAP prespecified subgroup analysis by Hb Target (i.e., 10-12 g/dL vs. 10-11 g/dL), this is not the same as the proposed subgroup analysis by PEP Hb level outlined above, which is considered post-hoc in nature.

The Agency is in agreement with the Sponsor's understanding of the ITT and PP definitions for MACE.

Question 1: Akebia has developed vadadustat tablets to support the proposed indication: TRADENAME [vadadustat tablets] is indicated for the treatment of anemia associated with CKD in adult patients on dialysis and not on dialysis. Does the Agency agree with the indication wording?

FDA Response to Question 1: No. The MACE analysis conducted in the 'not on dialysis' population did not demonstrate non-inferiority to darbepoetin. Therefore, pending review of the data, the indication would most likely be limited to patients with CKD on dialysis. In addition, the indication is a review issue based upon the review of the application and the patients enrolled in the trials. Please refer to Preamble above for more details.

Meeting Discussion: No further discussion took place during the meeting.

Question 2: Based on the overall NDA content plan, does the Agency agree that the planned submission appears materially complete, well organized, and would support acceptance for Filing?

FDA Response to Question 2: No. For Studies 0014, 0015, 0016, 0017, 0025, J01, J02, J03, and J04 you should also include the trial protocol (and all subsequent amendments) and statistical analysis plan (and all subsequent amendments). As discussed in our meetings, we would also like to remind you to include narratives for all patients in all conducted trials, who experienced SAEs (including MACE only adjudicated SAEs, Hy's law cases, patients who develop any malignancy during trial conduct and deaths) and who withdrew from study due to adverse reactions. In addition, CRFs must be provided for every patient for whom a narrative is written.
The NDA content plan for nonclinical as described in Appendix 4 of the briefing package appears complete to support the NDA submission for vadadustat.

We also refer you to the agreements during the meeting on February 11, 2020, regarding the content of the submission.

Meeting Discussion: No further discussion took place during the meeting.

Question 3: As required per 21 Code of Federal Regulations (CFR) § 54.2(e) and 54.3, Akebia has identified the key clinical studies that establish vadadustat's efficacy and those that contribute to the demonstration of vadadustat's safety. These studies are the four global Phase 3 studies (referred to as CI-0014, CI-0015, CI-0016, CI-0017). Akebia plans to submit the financial disclosure information for all clinical investigators that participated in these four studies only. Does the Agency agree that this approach meets the requirements and does not present a Filing issue?

FDA Response to Question 3: No, we recommend also submitting financial disclosure information for all randomized phase 2 studies (including those conducted in Japan) and the two randomized phase 3 studies conducted in Japan (i.e., J01 and J03). In the financial disclosure section submit the number of trial investigators who were Sponsor employees (full or part time).

Meeting Discussion: No further discussion took place during the meeting.

Question 4: Based on vadadustat's nonclinical reproductive toxicity profile and clinical experience to date, Akebia does not intend to establish a Pregnancy Exposure Registry for vadadustat upon Approval. Does the Agency agree?

FDA Response to Question 4: At this time, the Agency does not see the need for a pregnancy registry based upon the lack of one for other products for the same or similar indication. However, this could change based upon review of the non-clinical and clinical data submitted.

We recognize that the completed reproductive toxicology studies did not identify adverse effects for vadadustat. However, we do not necessarily agree that the use of vadadustat in pregnant women is without risk, as suggested in your comments. Rather consistent adverse effects on early embryofetal loss, viability, and growth are seen with other PHD inhibitors in development, some of which also echo findings in the labels for Epogen and Darbepoetin. There is literature linking HIF1 activity to placental development, and sustained HIF1 activity to human preeclampsia and restricted fetal growth, suggesting a potential mechanistic basis for the animal findings. Appropriate labeling and the need for mitigation, if any, will be evaluated during review of all relevant information submitted in your marketing application.

Meeting Discussion: No further discussion took place during the meeting.

Question 5: In preparation for the 120-day Safety Update post NDA submission, Akebia proposes a safety data cut-off date one month before NDA submission (NDA submission anticipated Q1 2021). This data cut-off date will allow for a minimum of 4 months additional safety data beyond the initial NDA safety data cut-off date (maximum of 6 months before submission date). Akebia does not plan to update the ISS or SCS but instead plans to provide the 120-day Safety Update report as a stand-alone report. Does FDA agree with this approach?

FDA Response to Question 5: Yes, this plan is acceptable.

Meeting Discussion: No further discussion took place during the meeting.

Question 6**:** Akebia plans to include the master validation plan, process validation reports, and commercial batch records (MBRs) for the 150 and 300 mg tablets

manufactured at [redacted] in the initial NDA. For the 450 mg tablets at [redacted] and the 150, 300 and 450 mg tablets at [redacted] the master validation plan, process validation protocols, and commercial MBRs will be available for any Agency planned Pre-Approval Inspection (PAI). Does the Agency agree that this approach is acceptable and does not present a Filing issue?

FDA Response to Question 6: Your proposed approach appears to be reasonable. In the initial NDA, be advised that a description of manufacturing procedures including, but not limited to, critical process parameters (CPPs), major equipment used, and in-process controls for manufacturing the drug product of all strengths and at all intended manufacturing sites be provided as per 21 CFR 314.50(d)(1)(ii).

Note that the FDA does not approve process validation protocols or reports during an application review. The actual protocols, acceptance criteria, study outcomes, and supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Meeting Discussion: No further discussion took place during the meeting.

Question 7: Does the Agency agree the Clinical Pharmacology program is complete and supports Filing of the planned NDA?

FDA Response to Question 7: Yes, the proposed Clinical Pharmacology program is acceptable.

Meeting Discussion: No further discussion took place during the meeting.

Question 8: Akebia conducted two Phase 3 studies as part of their INNO2VATE program (Studies CI-0016 and CI-0017) evaluating the efficacy and safety of once-daily oral vadadustat for the treatment of anemia in adult patients with DD-CKD. Based on the summary efficacy data from these studies, does the Agency agree that these studies met the prospective efficacy endpoints and these studies support the clinical efficacy of vadadustat for the treatment of anemia in CKD who are on dialysis?

FDA Response to Question 8: Yes. However, our final benefit/risk assessment is a review issue, based upon complete review of the application. Please refer to Preamble above for more details.

Meeting Discussion: No further discussion took place during the meeting.

Question 9: Akebia conducted two Phase 3 studies as part of their PRO2TECT program (Studies CI-0014 and CI-0015) evaluating the efficacy and safety of once-daily oral

vadadustat doses for the treatment of anemia in adult patients with NDD-CKD. Based on the summary efficacy data from these studies, does the Agency agree that these studies met the prospective efficacy endpoints and these studies support the clinical efficacy of vadadustat for the treatment of anemia in CKD who are not on dialysis?

FDA Response to Question 9: Yes. However, because the MACE safety endpoint was not non-inferiority, the benefit/risk may not appear positive. In addition, our final benefit/risk assessment is a review issue, based upon complete review of the application. Please refer to Preamble above for more details.

Meeting Discussion: No further discussion took place during the meeting.

Question 10: As part of the INNO2VATE program (Studies CI-0016 and CI-0017), the safety of once-daily oral vadadustat doses was assessed and compared to darbepoetin alfa (active comparator) for the treatment of anemia in adult patients with DD-CKD. Based on the summary safety data from these studies, does the Agency agree that these studies are sufficient to support NDA Filing of vadadustat for the treatment of anemia in CKD who are on dialysis?

FDA Response to Question 10: Yes. However, conclusions on satisfaction of filing requirements to support an indication will be based upon complete review of the application. Please refer to the Preamble above for more details.

Meeting Discussion: No further discussion took place during the meeting.

Question 11: As part of the PRO2TECT program (Studies CI-0014 and CI-0015), the safety of once-daily oral vadadustat doses was assessed and compared to darbepoetin alfa (active comparator) for the treatment of anemia in adult patients with NDD-CKD. Based on the primary MACE analyses of these studies, non-inferiority to darbepoetin was not achieved. However, pre-specified analyses of the US population, which is a randomization stratification factor, with a target Hb range of 10-11 g/dL revealed a HR that is not clinically meaningfully increased. To better understand the MACE data, Akebia plans to conduct additional MACE analyses for the NDA to support the indication of NDD-CKD in the US. Does the Agency agree that the additional analyses proposed below will support the Agency's review of the MACE data in the NDA and are there other analyses that would aid the Agency's review?

FDA Response to Question 11: Yes, the additional proposed analyses will support FDA's review of the Application. Whether the 'not on dialysis' population has a favorable benefit/risk assessment will remain a review issue. Please refer to Preamble above for more details.

Regarding the approach taken by McCullough 2013, we have the following comment: In general, data-driven model selection or model building is fraught with a variety of issues, including low probability of choosing the correct model,

underestimated standard errors, and biased estimates. In addition, including the chosen baseline characteristics as covariates rather than stratification factors in the Cox model makes the strong assumption of a common baseline hazard, which may not be met.

Meeting Discussion: No further discussion took place during the meeting.

Question 12: The safety evaluation of vadadustat oral tablets in support of chronic administration considered the number of subjects exposed and the duration of subject exposure to vadadustat throughout the clinical development program. Based on the summary exposure data presented herein, does the Agency agree subject exposure to vadadustat in the DD-CKD and NDD-CKD population is adequate and supports filing of the NDA?

FDA Response to Question 12: Yes, the population exposure is adequate for review of chronic administration of vadadustat.

Meeting Discussion: No further discussion took place during the meeting.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

The Sponsor stated that they will submit a complete application with no late submissions and that they intend to submit at end of Q1 2021.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation

Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

    - Regulations and related guidance documents.

    - A sample tool illustrating the format for Highlights and Contents, and

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

[5] https://www.fda.gov/media/85061/download

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's responses to the Agency's preliminary meeting comments are appended to these minutes.

MEETING INFORMATION

Product Name	Vadadustat (AKB-6548) tablets
Proposed Indication for Use	Treatment of anemia associated with chronic kidney disease in adult patients on dialysis and not on dialysis
Application #	IND #102465
Meeting Information	Type B Pre-NDA Meeting Date: October 29, 2020 Time: 8-9 AM Format: Teleconference
Sponsor	Name: Akebia Therapeutics, Inc. Address: 245 First Street, Suite 1100 Cambridge, Massachusetts 02142

FINAL LIST OF SPONSOR ATTENDEES

Please find below the final list of sponsor attendees:

Name	Title
Akebia Attendees	
Steven Burke	Sr Vice President, Research and Development and Chief Medical Officer
Geoff Ross	Sr Vice President, Clinical Development, Drug Safety, Pharmacovigilance, and Medical Affairs
Dennis Vargo	Vice President, Drug Safety and Pharmacovigilance
Youssef Farag	Director, Medical
Mike Collins	Sr Vice President, Clinical Operations and Data Sciences
Wenli Luo	Sr Director, Biostatistics
Molly E Shea	Vice President, Regulatory Affairs
Debleena Sengupta	Director, Regulatory Affairs
Otsuka Attendees	
Bob McQuade	Executive Vice President, Chief Strategic Officer
Charlotte Jones-Burton	Vice President, Global Clinical Development, Nephrology
Michael Fahmy	Sr Director, Global Regulatory Affairs
Catherine Sheppard	Director, Global Regulatory Affairs

EXECUTIVE SUMMARY - RESPONSE TO FDA PRELIMINARY COMMENTS

Akebia appreciates the Agency's preliminary comments dated 20 October 2020 to Akebia's questions for the Type B Pre-NDA Meeting. We have no further questions and or/comments with regards to Questions 1 to 12.

Akebia would like to discuss the Agency's Preamble and Discussion of the Content of a Complete Application preliminary responses at the pre-NDA meeting.

Please see our detailed responses to the FDA Preliminary Comments below:

FDA PREAMBLE

To evaluate the risk of cardiovascular AEs associated with vadadustat administration, a safety endpoint was defined for both the PRO2TECT program and the INNO2VATE program, as time to first MACE. Akebia powered its pivotal trial programs, in relation to both duration of treatment and sample size, to reach sufficient number of MACE per program, which was deemed adequate to provide statistical support to any non-inferiority conclusions resulting from the pivotal trials. In addition, there was agreement that successful demonstration of non- inferiority, in relation to active comparator (i.e. darbepoetin alfa), on both primary efficacy and primary safety endpoints will be necessary for approval for the proposed specific indication. As per summary efficacy results provided in the meeting package, you demonstrated non-inferiority for efficacy for patients with anemia associated with CKD, who were on dialysis and not on dialysis via Hemoglobin (Hb) endpoint. In addition, you demonstrated non-inferiority for the safety MACE endpoint for patients with anemia associated with CKD, who were on dialysis. However, the MACE analysis conducted in the 'not on dialysis' population did not demonstrate non-inferiority to darbepoetin.

We acknowledge you provided a summary of subgroup analysis results on the MACE endpoint for different regions, including US vs. Ex-US for the MACE primary and other key secondary endpoints. However, they are post-hoc findings. Due to concerns relating to insufficient power associated with subgroup sample size and inherent bias associated with multiplicity analyses without the presence of any mitigating strategy, we consider these results exploratory and hypothesis- generating in nature.

Whether you have demonstrated adequate evidence for the safety of vadadustat will ultimately be a review issue. To further evaluate the consistency across the studies and ensure the robustness of the results, in addition to analyses you conducted based on the pooled study data, please conduct key analyses for individual studies based on the intent-to-treat (ITT) population and Per-Protocol (PP) population regardless of whether the patient was on or off study treatment. Also, provide meta-analysis results by combining the estimates of hazard ratio (HR) from the Cox model of individual studies, and weights inversely proportional to the variance of the trial-specific log HR estimates to obtain an overall treatment effect.

Sponsor's Response to Preamble:

Clarification regarding regional analyses

Akebia appreciates the Agency's comments and understands the concerns regarding post-hoc analyses. The sponsor would like to clarify that the regional subgroup analyses, as well as other prespecified subgroup analyses, were not post-hoc but were prospectively defined for both the $INNO_2VATE$ and PRO_2TECT programs. Region (US, Europe, rest of world) was a stratification factor in the blocked randomization process in each study (i.e., the treatment groups are well balanced in each region), along with baseline hemoglobin and New York Heart Association

(NYHA) classification for heart failure. The analyses of efficacy and cardiovascular safety by stratification factors, target hemoglobin (10-11 g/dL for US and 10-12 g/dL for Europe and rest of world), and other covariates associated with the outcome measure were detailed in the MACE statistical analysis plan (SAP) provided in Appendix 7 of the pre-NDA briefing document. Thus, these analyses were prespecified and not post-hoc. Therefore, Akebia seeks agreement and modification of the Agency's preliminary responses to state that these analyses were prespecified.

Akebia will address the Agency's comments regarding power and multiplicity in the NDA.

Akebia acknowledges the Agency's request for an inverse-variance weighting meta-analysis and the results will be included in the NDA.

Clarification sought at the pre-NDA meeting

MACE analyses for the individual studies will be provided in the NDA. However, Akebia is seeking additional clarity around the Agency's statement regarding the intent-to-treat (ITT) and per protocol (PP) analyses in the third paragraph of the Preamble: *"To further evaluate the consistency across the studies and ensure the robustness of the results, in addition to analyses you conducted based on the pooled study data, please conduct key analyses for individual studies based on the intent-to-treat (ITT) population and Per-Protocol (PP) population regardless of whether the patient was on or off study treatment."*

Intention-to-Treat (ITT)

In INNO$_2$VATE, 21 patients were randomized but never received study medication. Three of these 21 patients experienced MACE events, all in the darbepoetin alfa group. In PRO$_2$TECT, five patients were randomized but never received study medication (see Figure 1 below). One of these 5 patients experienced MACE events. This patient was in the darbepoetin alfa group. If these 26 patients were added to the Safety population, this corresponds to the Agency's ITT population definition for the MACE analysis.

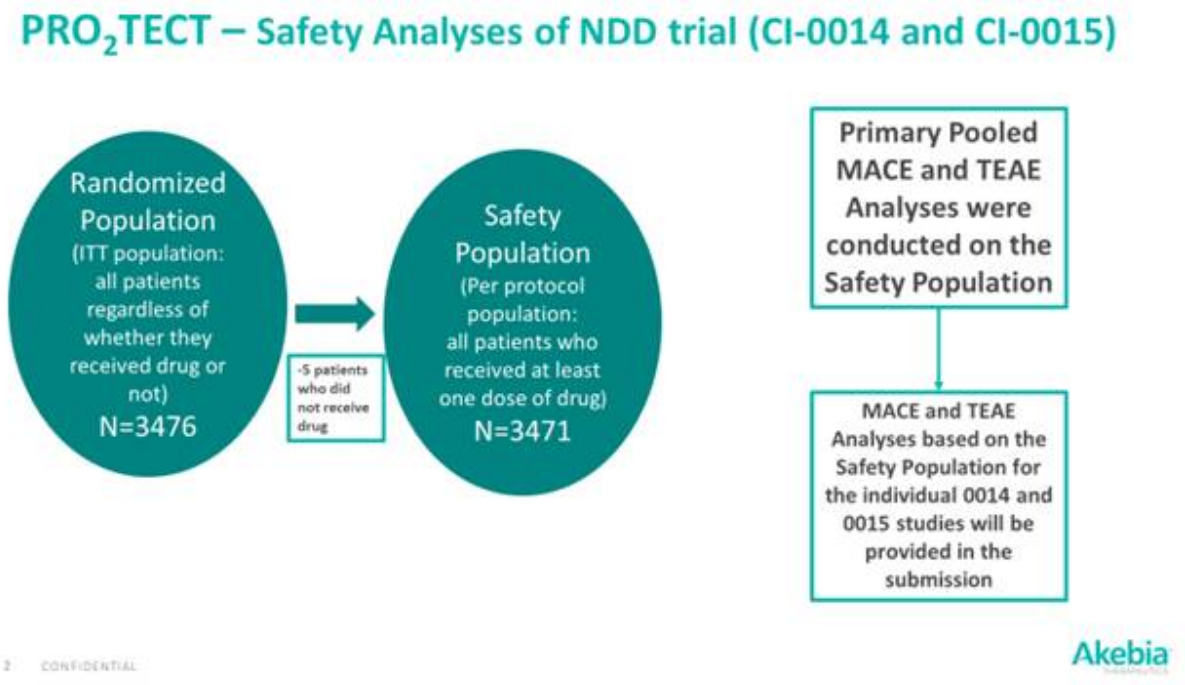
Is Akebia's understanding of the Agency's ITT definition for MACE is correct? If not, can the Agency clarify its definition of the ITT population for MACE?

Per Protocol (PP)

The MACE analysis was conducted in the Safety population which required a patient to have received at least a single dose of study medication (vadadustat or darbepoetin alfa, see Figure 1). Akebia's understanding is the Safety population corresponds to the PP population described in the preamble above for the MACE analysis.

Is Akebia's definition of the Safety population in line with the Agency's PP definition for MACE? If not, can the Agency clarify its definition of the PP population for MACE?

Figure 1: Akebia's understanding of the PP and ITT definitions illustrated by the PRO$_2$TECT study.



Question 1

Akebia has developed vadadustat tablets to support the proposed indication: TRADENAME [vadadustat tablets] is indicated for the treatment of anemia associated with CKD in adult patients on dialysis and not on dialysis. Does the Agency agree with the indication wording?

FDA Preliminary Response*:*
No. The MACE analysis conducted in the 'not on dialysis' population did not demonstrate non-inferiority to darbepoetin. Therefore, pending review of the data, the indication would most likely be limited to patients with CKD on dialysis. In addition, the indication is a review issue based upon the review of the application and the patients enrolled in the trials. Please refer to Preamble above for more details.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 2

Based on the overall NDA content plan, does the Agency agree that the planned submission appears materially complete, well organized, and would support acceptance for Filing?

FDA Preliminary Response*:*
No. For Studies 0014, 0015, 0016, 0017, 0025, J01, J02, J03, and J04 you should also include the trial protocol (and all subsequent amendments) and statistical analysis plan (and all subsequent amendments). As discussed in our meetings, we would also like to remind you to include narratives for all patients in all conducted trials, who experienced SAEs (including MACE only adjudicated SAEs, Hy's law cases, patients who develop any malignancy during trial conduct and deaths) and who withdrew from study due to adverse reactions. In addition, CRFs must be provided for every patient for whom a narrative is written.

The NDA content plan for nonclinical as described in Appendix 4 of the briefing package appears complete to support the NDA submission for vadadustat.

We also refer you to the agreements during the meeting on February 11, 2020, regarding the content of the submission.

Sponsor Response:
The sponsor acknowledges the Agency's feedback and will address these items in the NDA. No further discussion is required.

Question 3

As required per 21 Code of Federal Regulations (CFR) § 54.2(e) and 54.3, Akebia has identified the key clinical studies that establish vadadustat's efficacy and those that contribute to the demonstration of vadadustat's safety. These studies are the four global Phase 3 studies (referred to as CI-0014, CI-0015, CI-0016, CI-0017). Akebia plans to

submit the financial disclosure information for all clinical investigators that participated in these four studies only. Does the Agency agree that this approach meets the requirements and does not present a Filing issue?

FDA Preliminary Response*:*
No, we recommend also submitting financial disclosure information for all randomized phase 2 studies (including those conducted in Japan) and the two randomized phase 3 studies conducted in Japan (i.e., J01 and J03). In the financial disclosure section submit the number of trial investigators who were Sponsor employees (full or part time).

Sponsor Response:
The sponsor will provide the financial disclosure information for all the studies as requested by the Agency, as well the number of trial investigators who were sponsor employees (full or part time), if applicable. No further discussion is required.

Question 4

Based on vadadustat's nonclinical reproductive toxicity profile and clinical experience to date, Akebia does not intend to establish a Pregnancy Exposure Registry for vadadustat upon Approval. Does the Agency agree?

FDA Preliminary Response*:*
At this time, the Agency does not see the need for a pregnancy registry based upon the lack of one for other products for the same or similar indication. However, this could change based upon review of the non- clinical and clinical data submitted.

We recognize that the completed reproductive toxicology studies did not identify adverse effects for vadadustat. However, we do not necessarily agree that the use of vadadustat in pregnant women is without risk, as suggested in your comments. Rather consistent adverse effects on early embryofetal loss, viability, and growth are seen with other PHD inhibitors in development, some of which also echo findings in the labels for Epogen and Darbepoetin. There is literature linking HIF1 activity to placental development, and sustained HIF1 activity to human preeclampsia and restricted fetal growth, suggesting a potential mechanistic basis for the animal findings. Appropriate labeling and the need for mitigation, if any, will be evaluated during review of all relevant information submitted in your marketing application.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 5

In preparation for the 120-day Safety Update post NDA submission, Akebia proposes a safety data cut-off date one month before NDA submission (NDA submission anticipated Q1 2021). This data cut-off date will allow for a minimum of 4 months additional safety data beyond the initial NDA safety data cut-off date (maximum of 6 months before submission date). Akebia does not plan to update the ISS or SCS but instead plans to

provide the 120-day Safety Update report as a stand-alone report. Does FDA agree with this approach?

***FDA Preliminary Response**:*
Yes, this plan is acceptable.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 6

Akebia plans to include the master validation plan, process validation reports, and commercial batch records (MBRs) for the 150 and 300 mg tablets manufactured at (b) (4) in the initial NDA. For the 450 mg tablets at (b) (4) and the 150, 300 and 450 mg tablets at (b) (4), the master validation plan, process validation protocols, and commercial MBRs will be available for any Agency planned Pre-Approval Inspection (PAI). Does the Agency agree that this approach is acceptable and does not present a Filing issue?

***FDA Preliminary Response**:*
Your proposed approach appears to be reasonable. In the initial NDA, be advised that a description of manufacturing procedures including, but not limited to, critical process parameters (CPPs), major equipment used, and in-process controls for manufacturing the drug product of all strengths and at all intended manufacturing sites be provided as per 21 CFR 314.50(d)(1)(ii).

Note that the FDA does not approve process validation protocols or reports during an application review. The actual protocols, acceptance criteria, study outcomes, and supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 7

Does the Agency agree the Clinical Pharmacology program is complete and supports Filing of the planned NDA?

***FDA Preliminary Response**:*
Yes, the proposed Clinical Pharmacology program is acceptable.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 8

Akebia conducted two Phase 3 studies as part of their INNO2VATE program (Studies CI-0016 and CI-0017) evaluating the efficacy and safety of once-daily oral vadadustat for the treatment of anemia in adult patients with DD-CKD. Based on the summary efficacy data from these studies, does the Agency agree that these studies met the prospective efficacy endpoints and these studies support the clinical efficacy of vadadustat for the treatment of anemia in CKD who are on dialysis?

FDA Preliminary Response*:*
Yes. However, our final benefit/risk assessment is a review issue, based upon complete review of the application. Please refer to Preamble above for more details.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 9

Akebia conducted two Phase 3 studies as part of their PRO2TECT program (Studies CI-0014 and CI-0015) evaluating the efficacy and safety of once-daily oral vadadustat doses for the treatment of anemia in adult patients with NDD-CKD. Based on the summary efficacy data from these studies, does the Agency agree that these studies met the prospective efficacy endpoints and these studies support the clinical efficacy of vadadustat for the treatment of anemia in CKD who are not on dialysis?

FDA Preliminary Response*:*
Yes. However, because the MACE safety endpoint was not non-inferiority, the benefit/risk may not appear positive. In addition, our final benefit/risk assessment is a review issue, based upon complete review of the application. Please refer to Preamble above for more details.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 10

As part of the INNO2VATE program (Studies CI-0016 and CI-0017), the safety of once-daily oral vadadustat doses was assessed and compared to darbepoetin alfa (active comparator) for the treatment of anemia in adult patients with DD-CKD. Based on the summary safety data from these studies, does the Agency agree that these studies are sufficient to support NDA Filing of vadadustat for the treatment of anemia in CKD who are on dialysis?

FDA Preliminary Response*:*
Yes. However, conclusions on satisfaction of filing requirements to support an indication will be based upon complete review of the application. Please refer to the Preamble above for more details.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

Question 11

As part of the PRO2TECT program (Studies CI-0014 and CI-0015), the safety of once-daily oral vadadustat doses was assessed and compared to darbepoetin alfa (active comparator) for the treatment of anemia in adult patients with NDD-CKD. Based on the primary MACE analyses of these studies, non-inferiority to darbepoetin was not achieved. However, pre-specified analyses of the US population, which is a randomization stratification factor, with a target Hb range of 10-11 g/dL revealed a HR that is not clinically meaningfully increased. To better understand the MACE data, Akebia plans to conduct additional MACE analyses for the NDA to support the indication of NDD-CKD in the US. Does the Agency agree that the additional analyses proposed below will support the Agency's review of the MACE data in the NDA and are there other analyses that would aid the Agency's review?

FDA Preliminary Response*:*
Yes, the additional proposed analyses will support FDA's review of the Application. Whether the 'not on dialysis' population has a favorable benefit/risk assessment will remain a review issue. Please refer to Preamble above for more details.

Regarding the approach taken by McCullough 2013, we have the following comment: In general, data-driven model selection or model building is fraught with a variety of issues, including low probability of choosing the correct model, underestimated standard errors, and biased estimates. In addition, including the chosen baseline characteristics as covariates rather than stratification factors in the Cox model makes the strong assumption of a common baseline hazard, which may not be met.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion beyond the Preamble (see above) is required.

Question 12

The safety evaluation of vadadustat oral tablets in support of chronic administration considered the number of subjects exposed and the duration of subject exposure to vadadustat throughout the clinical development program. Based on the summary exposure data presented herein, does the Agency agree subject exposure to vadadustat in the DD-CKD and NDD-CKD population is adequate and supports filing of the NDA?

FDA Preliminary Response*:*
Yes, the population exposure is adequate for review of chronic administration of vadadustat.

Sponsor Response:
The sponsor acknowledges the Agency's response. No further discussion is required.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 23, 2020, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

Sponsor Response:
The sponsor acknowledges the Agency's response and will be prepared to discuss the contents of a full application, as well as any preliminary discussions regarding the need for REMS or other risk management actions, at the pre-NDA meeting.

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/

VIRGINIA E KWITKOWSKI
11/06/2020 01:20:50 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102465

MEETING MINUTES

Akebia Therapeutics, Inc.
Attention: Karen A. Jauregui
Senior Director, Regulatory Affairs
245 First Street
Suite 1100
Cambridge, MA 02142

Dear Ms. Jauregui:

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

We also refer to the meeting between representatives of your firm and the FDA on January 6, 2016. The purpose of the meeting was to discuss to discuss key elements of the clinical protocols for vadadustat for the use in patients with of anemia secondary to chronic kidney disease who are dependent on dialysis.

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

If you have any questions, call Janet G. Higgins, Regulatory Project Manager at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Medical Officer
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	January 6, 2016; 2:00 PM to 3:00 PM EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 102465
Product Name:	vadadustat
Indication:	for the treatment of anemia secondary to chronic kidney disease (CKD) in patients both on dialysis (DD-CKD) and not on dialysis (NDD-CKD)
Sponsor/Applicant Name:	Akebia Therapeutics, Inc.
Meeting Chair:	Tanya Wroblewski, MD
Meeting Recorder:	Janet G. Higgins

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)
Ann T. Farrell, MD, Director
Tanya Wroblewski, MD, Medical Officer
Janet G. Higgins, Regulatory Project Manager

Division of Biometrics V
Yuan Li Shen, DPH, Team Leader, Biostatistics
Qing Xu, PhD, Biostatistics Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Guoxiang Shen, PharmD, Clinical Pharmacologist

SPONSOR ATTENDEES

Karen Jauregui, BS, Senior Director, Regulatory Affairs
Mark A. De Rosch, PhD, Vice President, Regulatory Affairs
Brad Maroni, MD, Senior Vice President and CMO
Gurudatt Chandorkar, PhD, Director, Clinical Pharmacology
Valerie Waltman, MS, Associate Director, Regulatory Affairs
(b) (4)

(b) (4)

Jason Chan, PhD, Statistician, Akebia

1.0 BACKGROUND

Vadadustat(AKB-6548) is a small molecule inhibitor under development as a once daily oral treatment of anemia in patients with CKD. Akebia Therapeutics, Inc. (Akebia) is now developing vadadustat for the treatment of anemia secondary to chronic kidney disease (CKD) in patients both on dialysis (DD-CKD) and not on dialysis (NDD-CKD).

The objective of this meeting was to obtain feedback from the Division on the key elements of the Phase 3 clinical protocols for vadadustat for use in treatment of patients with anemia secondary to DD-CKD.

2. DISCUSSION

2.1. Clinical/ Statistical

Question 1: Does the Division agree that Study AKB-6548-CI-0016 and Study AKB-6548-CI-0017, together with data from the NDD-CKD studies AKB-6548-CI-0014 and AKB-6548-CI-0015, are appropriate for submission of a New Drug Application for treatment of anemia in patients with chronic kidney disease on dialysis and not on dialysis?

FDA Response to Question 1:
We have the following comments regarding your proposed studies in NDD-CKD populations:

- ***Clarify how many patients on peritoneal dialysis you intend to enroll in studies AKB-6548 CI-0016 and AKB-6548-CI-0017.***

The Division reiterates that the safety and efficacy data of vadadustat will be reviewed with regard to the entire program (DD-CKD and NDD-CKD). You need to meet both the primary efficacy and primary safety endpoints to conclude success.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 2: Does the Division agree with the primary efficacy endpoint for DD-CKD Study AKB-6548-CI-0016 and Study AKB-6548-CI-0017 as "Mean change in hemoglobin (HGB) between baseline (mean HGB from screening and baseline) and the primary evaluation period (mean HGB from weeks 24-36)" and the statistical analysis for the primary endpoint?

FDA Response to Question 2:
No.

Your primary endpoint is acceptable as is the primary evaluation period however the ITT population which includes all randomized subjects should be used for all efficacy analyses.

We note that you propose to use a value of zero for the missing value of the primary endpoint. However, we are concerned that such a single imputation method may cause bias if there were imbalance in the missing assessments between the two treatment groups or missing not at random. Please propose an alternative imputation method for the imputation if the number of missing data is large or data may not be missing at random.

Sensitivity analyses should be performed to examine the potential impact of the missing data. Additional sensitivity analyses based on different imputation scheme should be proposed. If the multiple imputation will be adopted, the details of the proposed missing data imputation scheme should be provided including computation methods (e.g. statements used SAS, including seed for random number generating procedure in the imputation). For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. An electronic version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955 a special report of the document can be found at http://www.nejm.org/doi/full/10.1056/NEJMsr1203730

Please provide detailed description of the primary efficacy analyses using ANOVA weighted by stratum size. Additional sensitivity analyses may be performed based on ANCOVA model adjusting for the baseline stratification factors.

Subgroup analyses such as age, gender, region and other important baseline characteristics should be also included in the protocol.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 3: Does the Division agree with the key secondary efficacy endpoints for the DD-CKD Phase 3 studies of:

- Mean change in HGB value between baseline (mean pretreatment HGB) and the secondary evaluation period (weeks 40-52);
- Proportion of subjects with mean HGB within the target range during the primary evaluation period (weeks 24-36);
- Mean weekly dose of IV elemental iron administered from baseline to week 52; and
- Proportion of subjects receiving red blood cell transfusion(s) from baseline to week 52?

FDA Response to Question 3: No, we recommend that the evaluation of mean change in hemoglobin between weeks 40-52 as your key secondary endpoint.

We do not agree with the endpoints of mean weekly dose of IV elemental iron or the proportion of subjects receiving red blood cell transfusions from baseline. These latter two endpoints are subjective, prone to bias and difficult to control. You will not be able to adequately balance for these endpoints in the study.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 4: Does the Division agree with the following inclusion criteria for the DD-CKD Phase 3 studies: serum ferritin ≥100 ng/mL OR transferrin saturation (TSAT) ≥20% at Screening?

FDA Response to Question 4:
No, we do not agree with your proposed inclusion criteria. Inclusion of subjects with CKD who do not receive adequate iron supplementation prior to enrollment into your trial is not acceptable.

Despite the limitations with the tests, the KDIGO working group recommends that supplemental iron should be administered to maintain ferritin levels > 200ng/mL in CKD hemodialysis patients and > 100ng/ml in CKD non-dialysis and peritoneal dialysis patients with TSAT > 20% in all patients.(KDIGO 2012).

In order to ensure that subjects with adequate iron repletion are enrolled in your study, we recommend that all patients meet the inclusion criteria of serum ferritin > 100ng/ml and transferritin saturation (TSAT) > 20%. Even patients with serum ferritin levels > 100ug/l and adequate bone marrow stores will have an increase in hemoglobin and/or reduction in current ESA dose with the use of supplemental iron(Kalantar-Zadeh 1995, Tessitore N 2001, Fishbane 1996, Fishbane 2001, Stancu 2010, Besarb 1999).

In addition, TSAT and ferritin levels should be monitored at least every 3 months during therapy with vadadustat and more frequent testing may be indicated in situations of blood loss or increasing or decreasing doses of vadadustat.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 5: Does the Division agree with the proposed stratification for the DD-CKD Phase 3 studies of:

- Geographic region (United States [US] vs European Union [EU] vs Rest of World [ROW]);
- New York Heart Association congestive heart failure (CHF) Class 0 or I vs II or III; and
- Baseline HGB (<9.5 vs ≥9.5 g/dL for Correction Study AKB-6548-CI-0016 and <10.5 vs ≥10.5 g/dL for Conversion Study AKB-6548-CI-0017)?

FDA Response to Question 5:
Your proposed stratification appears acceptable as long as results are consistent across regions.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 6: Does the Division consider the MACE non-inferiority margin of 1.25 (upper bound of the 2-sided 95% confidence interval for the hazard ratio) acceptable to characterize the cardiovascular safety of vadadustat in 2,600 patients with DD-CKD (total treatment period of 36 months and a mean exposure ~18 months) in support of the NDA for DD-CKD indication?

FDA Response to Question 6:
Your proposed approach to assess the comparative cardiovascular safety of vadadustat to include your proposed MACE NI margin appears reasonable based on our current understanding.

Your sample size calculation should also consider dropout rate. Provide justification of parameters that you used for the sample size calculation. Please include details (e.g., formulae or literature references) for the approaches in determining the sample size.

A detailed analysis plan for MACE endpoint should be provided including the censoring scheme. Sensitivity analyses that consider early drop out, taking rescue medication and missing MACE endpoint assessment, etc, using different censoring schemes, should also be provided. The Statistical Analysis Plan (SAP) for analyses of MACE endpoint should include an investigation of the proportionality of hazard assumption and a description of how to handle the case when the assumption is not satisfied.

Please submit statistical analysis plan for combined analyses for study AKB-6548 CI-0016 and AKB-6548-CI-0017. These combined analyses should be stratified by study.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 7: Does the Division agree with the proposed starting dose and the dose-adjustment algorithm for use in Study AKB-6548-CI-0016 and Study AKB-6548-CI-0017?

FDA Response to Question 7:
While the proposed starting dose of 300 mg once daily and dose-adjustment algorithm appears reasonable, we do not agree with your target hemoglobin levels. The target hemoglobin level must be identical between the US and non-US populations. Any difference in target levels will confound the interpretability of the safety and efficacy results of the studies

Discussion:
The Agency does not agree with the proposed target range of 10 to 12 g/dL for the global dialysis-dependent population. The upper limit of the target Hgb must be consistent with a USPI for Epogen/Procrit. The target hemoglobin level must be the same between the US and the non-US populations.

Question 8: Does the Division agree with the proposed informative sparse pharmacokinetic sampling scheme planned for the Phase 3 DD-CKD studies to support submission of the NDA for vadadustat?

FDA Response to Question 8:
While we agree with proposed sparse PK sampling strategy, please outline the actual time points for PK assessment at the proposed visits in the Phase 3 protocols.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Additional Clinical Pharmacology Comments:
Regarding the development of vadadustat, we have the following recommendations:

1. ***Based on in vitro DDI assessment and observed exposures at the therapeutic doses, vadadustat and its major O-glucuronide metabolite have potential to inhibit CYP2C8, CYP2C9, CYP2B6, and UGT1A1. Both vadadustat and O-glucuronide metabolite also have potential to inhibit human efflux transporters (P-gp and BCRP) and uptake transporters (OATP1B1, OAT1 and OAT3) at therapeutic concentrations. Please conduct further evaluations to accurately determine the magnitude of in vitro DDI in order to determine the need for clinical DDI studies. Refer to the Drug Interaction Studies Guidance for more information.***
2. ***Based on your human ADME study evaluation you will need to conduct hepatic impairment study.***

Additional Clinical Comments:
FDA considers US-licensed Epogen/Procrit as product that carries the US-licensed Epogen/Protcrit label and license number. Products that do not carry the US-licensed Epogen/Procrit label and license number are not considered US-licensed Epogen/Procrit regardless of the origin of such products.

We encourage the use of US-licensed Epogen/Procrit for your comparator arm because we know the safety, purity, and potency of US-licensed Epogen/Procrit.

If you choose to use US-licensed Epogen/Procrit at certain study sites and non-US-licensed epoetin alfa at other study sites for the active comparator arm of your clinical trial(s), you would need to establish an adequate scientific bridge to justify the relevance of data obtained with non-US-licensed epoetin alfa. With respect to your development program, the type of bridging data that may be needed to provide adequate scientific justification for this approach would include data from direct, comparative analytical studies (e.g. structural and functional data) of US-licensed Epogen/Procrit and non-US-licensed epoetin alfa, and is likely to also include bridging clinical PK study data. The comparisons should meet the pre-specified acceptance criteria for analytical and PK similarity. You may submit publicly available information regarding non-US-licensed epoetin alfa to justify the extent of comparative data needed to establish a bridge to US-licensed Epogen/Procrit. The complexity of the product, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of

heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. You should address any other factors that may affect the extent of bridging data to support such an approach.

In addition, we recommend that you compare the safety, efficacy, and dosing of US-licensed Epogen/Procrit with non-US-licensed epoetin alfa products used in the clinical trial. Differences in the safety, efficacy, and dosing profile of US-licensed Epogen/Procrit with other non-US-licensed epoetin alfa products may affect the Agency's ability to interpret the results of your clinical trial. The adequacy of this scientific justification and bridge would be a review issue.

Please note, however, that the use of US-licensed Epogen/Procrit and non-US-licensed epoetin alfa as active comparators in a clinical trial may have labeling implications should the data generated using multiple comparator products are necessary to support approval.

Discussion:
A scientific bridge consisting of comparative analytical studies (e.g. structural and functional data) of US-licensed Epogen/Procrit and non-US-licensed epoetin alfa, and is likely to also include bridging clinical PK study data. The comparisons should meet the pre-specified acceptance criteria for analytical and PK similarity. You may submit publicly available information regarding non-US-licensed epoetin alfa to justify the extent of comparative data needed to establish a bridge to US-licensed Epogen/Procrit. The complexity of the product, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. You should address any other factors that may affect the extent of bridging data to support such an approach.

The Agency suggested that the Sponsor may wish to discuss their scientific bridging proposal more fully and recommended submission of the bridging proposal prior to initiating the Phase 3 studies in the DD-CKD population to help facilitate the development plan for vadadustat in this population.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance

below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A (a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

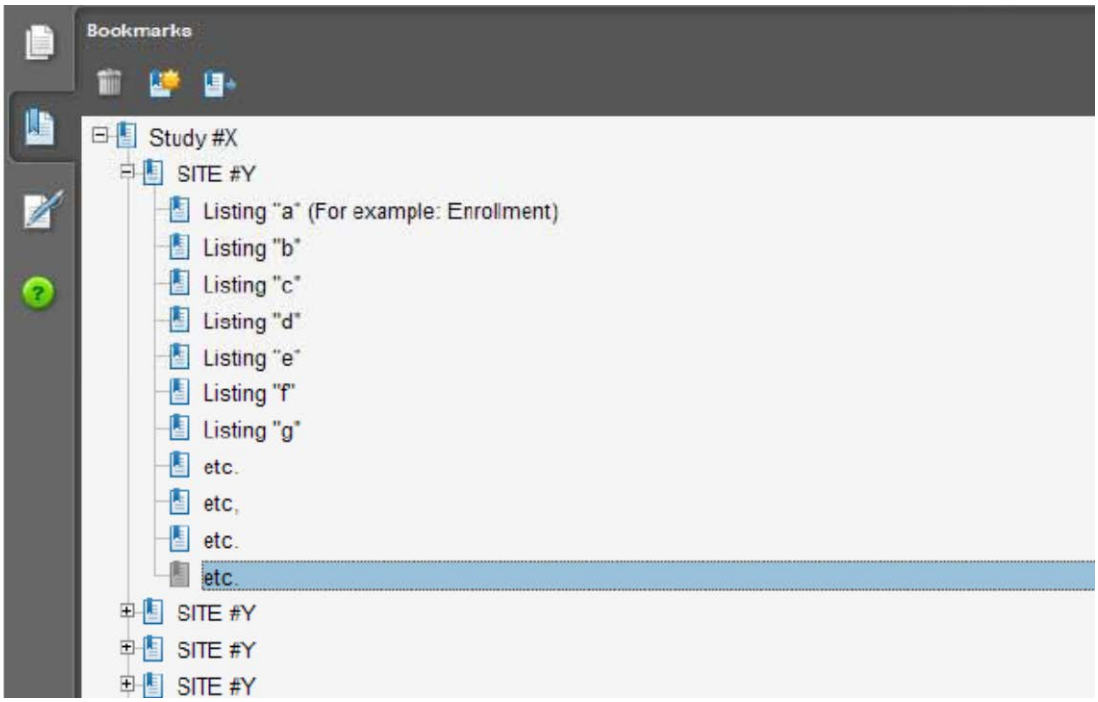
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into

this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the article discussed at the meeting is attached.

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/s/

TANYA M WROBLEWSKI
01/12/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND102465

MEETING MINUTES

Akebia Therapeutics, Inc.
Attention: Mark A. De Rosch, Ph.D.
Vice President, Regulatory Affairs
245 First Street, Suite 1100
Cambridge, MA 02142

Dear Dr. De Rosch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AKB-6548.

We also refer to the telecon between representatives of your firm and the FDA on July 16, 2015. The purpose of the meeting was to discuss regulatory starting materials, specifications for registration stability batches for drug substance and drug product, and elements of the drug product manufacturing process.

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

If you have any questions, call Rabiya Laiq, Pharm.D, Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	July 16, 2015 from 2:00 PM- 3:00 PM
Meeting Location:	Teleconference
Application Number:	IND 102465
Product Name:	AKB-6548
Indication:	Anemia associated with Chronic Kidney Disease & Renal Failure
Sponsor/Applicant Name:	Akebia Therapeutics, Inc.
Meeting Chair:	Janice Brown, M.S.
Meeting Recorder:	Rabiya Laiq, Pharm.D.

FDA ATTENDEES
Janice Brown, M.S., Quality Assessment Lead
Nina Ni, Ph.D., Quality Drug Product Reviewer
Gene W Holbert, Ph.D., API Reviewer
Peter Guerrieri, Ph.D., Drug Process/ Micro Reviewer
Pedro DelValle, Ph.D., Pharmacology/Toxicology Reviewer
Rabiya Laiq, Pharm.D., Regulatory Business Process Manager
Christopher Sheth, Ph.D., Pharmacology/Toxicology Supervisory Reviewer

SPONSOR ATTENDEES
Mark A. De Rosch, PhD, Vice President, Regulatory Affairs
Roger Hanselmann, PhD, Director, Process Research and Development
Karen Jauregui, BS, Senior Director, Regulatory Affairs
(b) (4)

1.0 BACKGROUND

The purpose of meeting was to discuss regulatory starting materials, specifications for registration stability batches for drug substance and drug product, and elements of the drug product manufacturing process. FDA sent Preliminary Comments to Akebia on July 9, 2015.

2. DISCUSSION

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/s/

RABIYA LAIQ
07/17/2015

JANICE T BROWN
07/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102465

MEETING MINUTES

Akebia Therapeutics, Inc.
Attention: Mark A. De Rosch, PhD
Vice President, Regulatory Affairs
245 First Street
Suite 1100
Cambridge, MA 02142

Dear Dr. De Rosch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AKB-6548.

We also refer to the meeting between representatives of your firm and the FDA on July 7, 2015. The purpose of the meeting was to discuss the design of the two Phase 3 studies, the clinical pharmacology/biopharmaceutics plan, and the nonclinical development plan.

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

If you have any questions, call Janet G. Higgins, Regulatory Project Manager at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Slide Presentation

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	July 7, 2015; 3:00 PM to 4:00 PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 102465
Product Name:	AKB-6548
Indication:	for the treatment of anemia in patients with non-dialysis dependent chronic kidney disease (NDD-CKD)
Sponsor/Applicant Name:	Akebia Therapeutics, Inc. (Akebia)
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Janet G. Higgins

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)
Ann T. Farrell, MD, Director
Robert Kane, MD, Deputy Director for Safety
R. Angelo de Claro, MD, Clinical Team Leader
Kathy Robie-Suh, MD, PhD, Clinical Team Leader
Tanya Wroblewski, MD, Medical Officer
Vishal Bhatnagar, MD, Medical Officer
Janet G. Higgins, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology (DHOT)
Christopher Sheth, PhD, Pharmacology/Toxicology Supervisor
Pedro L. Del Valle, PhD, Pharmacologist

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader
Vicky Hsu, PharmD, Clinical Pharmacologist

Division of Pharmacometrics
Nitin Mehrotra, PhD, Pharmacometrics Team Leader
Dhananjay Marathe, Pharmacometrics Reviewer

Division of Biometrics V
Yuan Li Shen, PhD, Team Leader, Biostatistics
Qing Xu, PhD, Biostatistics Reviewer

SPONSOR ATTENDEES
Mark A. De Rosch, PhD, Vice President, Regulatory Affairs, Akebia
Brad Maroni, MD, Senior Vice President and CMO, Akebia
Charlotte Hartman, PharmD, Vice President, Clinical Research, Akebia
Sarb Shergill, PhD, Vice President, Clinical Development Operations, Akebia
Akshay Buch, PhD, Director, Clinical Pharmacokinetics, Akebia
Karen Jauregui, BS, Senior Director, Regulatory Affairs, Akebia
Rachel McElligott, MS, Regulatory Affairs Specialist I, Akebia
(b) (4)

The following Akebia representatives attended by teleconference:

Paul Vancutsem, DVM, PhD, Senior Director, Toxicology and DMPK, Akebia
Brandi Soldo, PhD, DABT, Senior Director, Toxicology, Akebia
Diana Lamppu, BA, Senior Director, Global Program Management, Akebia
John P. Butler, MBA, President and CEO, Akebia

1.0 BACKGROUND

AKB-6548 is a small molecule inhibitor under development as a once daily oral treatment of anemia in patients with CKD. Initially, Akebia intends to develop AKB-6548 for the treatment of anemia in patients with non-dialysis dependent chronic kidney disease (NDD-CKD). The Sponsor plans on submitting a supplemental New Drug Application for AKB-6548 for the treatment of anemia in patients with dialysis-dependent CKD (DD-CKD).

The objective of this meeting was to seek agreement with the Division on the design of the Phase 3 clinical trial program, the clinical pharmacology plan, and the nonclinical development plan to support a New Drug Application (NDA) for use of AKB-6548 for treatment of anemia in patients with chronic kidney disease not on dialysis.

2. DISCUSSION

2.1. Non-Clinical

Question 1: ***Does the Division consider the type and duration of the nonclinical safety and toxicology studies to likely be adequate to support submission of a New Drug Application for AKB-6548?***

FDA Response to Question 1:
Your nonclinical program appears to be adequate to support an NDA application.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

2.2. Clinical

Question 2: ***Does the Division agree that Study AKB-6548-CI-0014 and Study AKB-6548-CI-0015 are appropriate for submission of a New Drug Application for treatment of anemia in patients with chronic kidney disease not on dialysis, supported with safety data from ongoing Phase 3 studies in patients on dialysis?***

FDA Response to Question 2:
No, we do not agree with your non-inferiority margin for studies AKB-6549-CI-0014 and Study AKB-6548-CI-0015. See response to question 6.

We strongly recommend the results of Phase 3 studies be submitted at the same time for both dialysis dependent and non-dialysis dependent CKD population. Ultimately, the safety and efficacy of AKB-6548 will be reviewed with regard to the entire program (dialysis and non-dialysis populations). The Agency's opinion is that you need the data from both populations (dialysis and non-dialysis populations) to support either indication.

You need to meet both the primary efficacy and primary safety endpoints to conclude success.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 3: ***Does the Division agree with the primary endpoint "Mean change in Hgb between baseline (mean Hgb from screening and baseline) and the primary evaluation period (mean Hgb from weeks 24-36)" and the statistical analysis for the primary endpoint?***

FDA Response to Question 3:
It is noted that ITT population which includes all randomized subjects should be used for all efficacy analyses. Please note that the number of patients not being evaluated for the primary and key secondary efficacy and safety endpoints should be kept to a minimum. Too much missing data will undermine the reliability and confidence of the results. Sensitivity analyses should be performed to examine the potential impact of the missing data. Additional sensitivity analyses based on different imputation schemes should be proposed. If the multiple imputation will be adopted, the details of the proposed missing data imputation scheme should be provided including computation methods (e.g statements used SAS, including seed for random number generating procedure in the imputation). For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. An electronic

version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955 A special report of the document can be found at http://www.nejm.org/doi/full/10.1056/NEJMsr1203730

Please provide detailed description of the primary efficacy analyses using ANOVA weighted by stratum size. Additional sensitivity analyses may be performed based on ANCOVA model adjusting for the baseline stratification factors.

One of the issues your proposal raises is that subjects will be allowed to have their Hgb rescued with ESA therapy or transfusion. For statistical analysis purpose, FDA considers rescue therapy may confound the analysis of the results. Please discuss your proposals for handling this issue.

Provide justification of parameters that you used for the sample size calculation. Please include details (e.g, formula or literature references) for the approaches in determining the sample size.

The Statistical Analysis Plan (SAP) should include an investigation of the proportionality of hazard assumption and a description of how to handle the case when the assumption is not satisfied.

Subgroup analyses such as age, gender, region and other important baseline characteristics should be also included in the protocol.

We also recommend that the evaluation of mean change in hemoglobin between weeks 40-52 is your key secondary endpoint. We reiterate that the durability of mean change in hemoglobin for the entire duration of the study will be an important review issue.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 4: ***Does the Division agree with the key secondary endpoints for the NDD-CKD Phase 3 studies of:***

- ***Proportion of subjects with mean Hgb between 10.0 and 12.0 g/dL (inclusive) during the primary evaluation period (weeks 24-36);***
- ***Mean cumulative of IV elemental iron administered from baseline to week 52; and***
- ***Proportion of subjects receiving red blood cell transfusion(s) from baseline to week 52?***

FDA Response to Question 4:
No, we recommend that the evaluation of mean change in hemoglobin between weeks 40-52 is your key secondary endpoint.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 5: ***Does the Division agree with the proposed stratification for the NDD-CKD Phase 3 studies of:***

- ***Geographic region (United States [US] vs European Union [EU] vs Rest of World [ROW];***
- ***New York Heart Association congestive heart failure (CHF) Class 0 or I vs II or III; and,***
  Baseline Hgb (<9.5 vs ≥9.5 g/dL for Correction Study AKB-6548-CI-0014 and <10.5 vs ≥10.5 g/dL for Conversion Study AKB-6548-CI-0015)?

FDA Response to Question 5: Yes. A stratification plan by region is acceptable if the results are consistent across regions. Include in the SAP a measure to assess consistency across regions and analysis methods that will be used in the event that regions yield conflicting results.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 6: ***Does the Division agree with the proposed pooled MACE safety analysis plan?***

FDA Response to Question 6:
No, we do not agree the non-inferiority margin of 1.3 relative risk for pooled MACE endpoint. Your rationale included composite endpoints from the NHS, Choir and TREAT trials. We recommend that you look at the MACE results from the FDA's October 18th 2010 CRDAAC briefing document to help guide your proposed non-inferiority margin for MACE.

The safety analysis based on pooled study for MACE endpoint should be stratified by each study.

Provide sensitivity analyses for the primary safety MACE endpoint in the protocol, which includes different censoring rules for the analyses of time-to-event endpoints. The sensitivity analyses should consider the events in which patients missing assessments, lost-to-follow-up and taking rescue medication in the statistical analysis plan.

We note that the types of patients recruited, types of events seen, rapidity of MACE event accrual and the distribution of MACE events will impact the overall interpretation of safety results of your study. For example, an imbalance in the frequency of secondary endpoints (e.g. increased hospitalization for heart failure) compared to a neutral MACE finding will be a challenge in the interpretation of the overall benefit risk profile of your drug.

Discussion:
The Sponsor acknowledged the Agency's comments. The Sponsor noted that defining the non-inferiority margin is challenging.

The Agency noted the following issues with the overall development plan which limits the Agency's assessment of the Sponsor's proposal for the non-inferiority margin:
1. Inadequate statistical and clinical reasoning provided in selection of the non-inferiority margin
2. Lack of replication of trial results within the same proposed indication
3. Proposed timing of submissions to submit information initially on the non-dialysis-dependent (NDD) only, with information on dialysis-dependent (DD) population to follow as a supplemental application
4. Selection of Phase 3 dose in the meeting package was not adequately justified.
5. Use of target hemoglobin levels that are not consistent with the US prescribing information for ESAs
6. Cardiovascular safety issue noted in AKB-6548 treated patients in the Phase 2 trials

In addition, the Agency recommended that safety should be adequately assessed for the NDD and DD populations separately.

Question 7: ***Does the Division agree with the starting dose and the dose-adjustment algorithm for use in Study AKB-6548-CI-0014 and Study AKB-6548-CI-0015?***

FDA Response to Question 7:
No, we recommend you to conduct additional simulations to justify the dosing regimen to target Hgb level of 10-11 g/dL. Your modeling and simulation results generally suggest an increase in Hgb level by ~1.4 g/dL on a median level with the 450 mg once daily (QD) dosing. These simulations were carried out with the hemoglobin target range of 10-12 g/dL. Given that the range of Hgb levels to be targeted is 10-11 g/dL , the 450 mg QD dosing will likely lead to a lot of down-titrations and may result in significant proportion of patients outside this target range for a period of time till they reach their optimal dose. Thus, the information and supporting data provided in the meeting package is inadequate to justify the proposed starting dose and dose-adjustment algorithm for the phase 3 trials.

One possible approach could be to conduct the following simulations to further refine and justify your phase 3 dosing:
i) Choose the hemoglobin target range of 10-11 g/dL instead of 10-12 g/dL.
ii) Choose alternative starting dose of 300 and 150 mg QD in addition to 450 mg QD and carry out simulations with scenarios of fixed dosing as well as appropriate titrations for dosing changes to quantify the population level expected outcomes.
iii) Quantify the distribution of final stable dose levels, time to reach optimal stable dose and percentage of population within and outside the desired Hgb target range of 10-11 g/dL
iv) Utilize separate scenarios for correction vs. conversion trial with the appropriate baseline Hgb levels for the corresponding population to be enrolled, in order to justify the starting dose and dosing algorithm in each population, separately. Explore possibility of different starting doses depending on baseline Hgb levels.

Finally, it is unclear why AKB-6548-CI-0007 results were not incorporated in the PK/PD modeling. If possible, utilize the data from this study to inform/evaluate your PK/PD model in order to have more robust simulated predictions.

Discussion:
The Sponsor presented their slides and revised proposal regarding dosing in the Phase 3 trials. The Agency recommended that the Sponsor submit the simulations, datasets, and model codes for Agency review.

Post Meeting Comment:
In general, the new approach to selection of starting dose seems reasonable. Please submit the results of simulations as suggested in the pre-meeting response above (distribution of final stable doses, number of dose changes encountered for different starting doses, effect of baseline Hgb etc.) and any other relevant information to evaluate the appropriateness of selection of phase 3 dosing. If possible, also submit the model codes and datasets for simulations for our evaluation.

Question 8: Does the Division agree with the proposed informative population pharmacokinetics sampling scheme planned for the Phase 3 studies to support submission of the NDA for AKB-6548?

FDA Response to Question 8:

We recommend that you include PK sampling at Week 4 (or Week 2) in your study design in order to minimize drop-out or bias in sampling for exposure-response analyses. Also, we recommend that you collect the PK samples from all the subjects in your Phase 3 Studies.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

2.3. Clinical Pharmacology

Question 9: Does the Division agree that the proposed clinical pharmacology plan is appropriate to support submission of the NDA for AKB-6548?

FDA Response to Question 9:

We re-iterate our comment that an in vivo drug interaction trial with a P-gp substrate is warranted (from Type C meeting, 07/11/14). Additionally, based on your in vitro DDI results, it appears in vivo drug interaction trials with BCRP, OAT1, OAT3, and CYP2C8 sensitive substrates are also warranted. Please review the Drug Interaction Studies Guidance regarding which in vivo studies should be conducted to evaluate the drug-drug interaction potential of AKB-6548 and its metabolites. If you intend to use population PK approach to evaluate DDI (e.g., effect of OATP1B1, OATP1B3 and UGT1A1 inhibitors

on AKB-6548 PK), then you should design the Phase 3 Studies prospectively to ascertain that the potential interaction effects can be adequately detected.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 10: (b) (4)

(b) (4)

FDA Response to Question 10:

(b) (4)

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Additional Comments:

1. Your entry criteria for non-dialysis ESA users is too high. We recommend enrolling patients on your maintenance study (AKB-6548-CO-0015) with baseline hemoglobin levels between 8-11.0g/dL.
2. We note the asymmetry of rescue therapy between treatment arms would confound the interpretation of your non-inferiority trials. Please describe your approach to address this issue.
3. Ensure that US subjects account for at least 30% of the total population enrolled in your phase 3 trials in order for the results to be applicable to the US population.
4. Clarify the assessment window to be used in analysis of MACE events, specifically inclusion of MACE events after discontinuation of study drug.
5. There were 3 deaths in the treatment arm of your phase 2b Study (AKB-6548-CI-0007) that occurred between week 5 and week 20 due to ischemic heart disease, sudden cardiac death and cardiac arrest and there were no deaths in the placebo arm. Although you and the study

attribute the deaths as not related to the study drug, the agency considers these three deaths alarming.

6. Exclude patients with MI within < 12 weeks.
7. The Agency reminds you to follow current FDA approved labeling recommendations for ESA's dosing initiation and target hemoglobin levels. A safe hemoglobin target has not been established for ESA products in patients with CKD.

Discussion:
The Sponsor acknowledged FDA's comments, no discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development

lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the discussion.

6.0 ATTACHMENTS AND HANDOUTS

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/s/

ROMEO A DE CLARO
07/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102465

MEETING MINUTES

Akebia Therapeutics, Inc.
Attention: Robert Shalwitz, M.D.
Sr. Vice President and Chief Medical Officer
9987 Carver Road, Suite 420
Cincinnati, OH 45242

Dear Dr. Shalwitz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AKB-6548.

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2012. The purpose of the meeting was to reach an agreement on the design of your pivotal Phase 2b controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision to advance to a Phase 3 trial in support of market approvability.

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

If you have any questions, call Tyree Newman at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, M.D.
Clinical Team Leader, Hematology
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 1, 2012
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	102465
Product Name:	AKB-6548
Indication:	Treatment of anemia associated with (b) (4) (b) (4) (b) (4) patients with chronic kidney disease (CKD)
Sponsor/Applicant Name:	Akebia Therapeutics Inc.
Meeting Chair:	Albert Deisseroth, M.D.
Meeting Recorder:	Tyree Newman, B.S.

FDA ATTENDEES

Division of Hematology Products (DHP)

Ann Farrell, M.D., Director (Acting)
Albert Deisseroth, M.D., Clinical Team Leader, Hematology
Saleh Ayache, M.D., Clinical Reviewer
Tyree Newman, B.S., Regulatory Health Project Manager
Diane Leaman, B.S., Safety Regulatory Project Manager

Division of Biometrics V (DBV)

Qing Xu, Ph.D., Biostatistics Reviewer
Mark Rothmann, Ph.D., Biostatistics Team Leader

SPONSOR ATTENDEES

Robert Shalwitz, M.D.; Sr. Vice President and Chief Medical Officer, Akebia Therapeutics, Inc.
Kevin Peters, M.D., C.S.O. and V.P. R&D, Akebia Therapeutics, Inc.
Joseph Gardner, Ph.D., President and C.E.O., Akebia Therapeutics, Inc.
Charlotte Hartman, Pharm.D.; Director, Clinical Sciences, Akebia Therapeutics, Inc.
Brandi Soldo, Ph.D., D.A.B.T., Director of Toxicology, Akebia Therapeutics, Inc.
Cindy Flinn, M.S., Director, Project Planning, Akebia Therapeutics, Inc.
(b) (4)

AkshayBuch, Director, Clinical PK, Akebia Therapeutics, Inc.
(b) (4)

1.0 BACKGROUND

On February 2, 2012, the Agency received a Type B meeting request from Akebia Therapeutics. The Agency granted the meeting request on February 13, 2012.

The purpose of this meeting with the Agency was to discuss and reach an agreement on the design of the pivotal Phase 2b controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision to advance to Phase 3 trials in support of market approvability.

The meeting package was received on April 2, 2012. On April 25, 2012, the Agency sent to Akebia Therapeutics by email the preliminary responses to the questions contained in the meeting information package dated March 30, 2012.

2. DISCUSSION

2.1. Clinical

Question 1: AKB-6548-CI-0007 is a Phase 2b, randomized, double-blind, placebo-controlled study to assess the hematologic pharmacodynamic response, safety, and tolerability of orally administered AKB-6548 during repeat dosing for 16 weeks (112 days) in subjects with anemia associated with Stages 3, 4 and 5 CKD. Target enrollment in this study will be 120 subjects with Stages 3, 4 or 5 (pre-dialysis) CKD. Subjects will be randomized in accordance with: 1) hemoglobin at baseline; and, 2) ESA status. This study will allow for dose adjustment based on regular HGB measurements to help ensure that the subject reaches and/or maintains a target hemoglobin of (b) (4) *g/dL, or has a minimum increase of 1.2 g/dL if baseline HGB is ≤9.7 g/dL.*

Does the Division concur with the proposed clinical study design (as more fully described in attached synopsis)?

FDA Response: No, the proposed approach is not acceptable. We recommend a revision to the design, eligibility criteria, and endpoints of the trial. The primary endpoint of targeting a hemoglobin range (b) (4) **g/dL should be revised to a change in hemoglobin level from baseline and not a specific hemoglobin level. The eligibility criterion of hemoglobin level for naïve patients of** (b) (4) **g/dL should be revised to include patients with hemoglobin less than 10 g/dL for entry. The definition of "ESA naïve patient" should exclude patients who have had any prior exposure to ESAs.**
The definition of "success" should be further clarified, and preferably consist of a desired change from baseline rather than a specific target range. The study design should provide dosing that achieves hemoglobin values consistent with the current labeling of ESAs or justify any differences. Please justify in your Target Product Profile (TPP) the hemoglobin of (b) (4) **g/dL rather than the level described in the ESA labels. Define what you mean by clinically significant worsening of anemia or symptoms of anemia (p. 96).**

Discussion: ***The Sponsor and Agency had a wide-ranging discussion regarding the Sponsor's development plans for AKB-6548. The Agency does not object to the Sponsor conducting a limited duration phase 2b study, however, the Agency recommended that the Sponsor consider their phase 3 trial design when designing the phase 2b study (e.g., endpoints).***

Question 2: The planned Phase 3 program will include two (or more) randomized, placebo controlled, pivotal clinical trials modeled after the Phase 2b study. The primary objectives of the studies will be to demonstrate that treatment of anemia associated CKD with AKB-6548 will: 1) safely increase HGB and maintain it in a target range of 11.0 - 12.0 g/dL; 2) be non-inferior to placebo for cardiovascular safety events; and, 3) decrease symptoms of depressed mood, cognitive dysfunction, and fatigue. The investigational approach for the Phase 2b study has been designed to mimic the planned Phase 3 program, and eventual approved use in the clinical environment.

Does the Division concur with this approach and that the Phase 2b study as designed will support a Phase 3 program of similar design?

FDA Response: No. As summarized in the answer to Question #1 (see above), the proposal to maintain the hemoglobin in the (b) (4) g/dL range is in conflict with the recommendations in the current label for ESAs and is therefore unacceptable. In addition, more details on your approach for demonstrating non-inferiority to placebo for cardiovascular safety will be necessary in order for the FDA to comment. The FDA cannot evaluate the proposal to use the patient reported outcomes of depressed mood, cognitive dysfunction and fatigue without a more detailed proposal. The Sponsor is referred to the FDA Guidance: Patient Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims. When a more detailed plan for the PRO and the results of the proposed collection of qualitative and quantitative evidence to support the cognitive performance of the 3 proposed PRO endpoints are available for submission, the FDA will review the proposal. The acceptability of the phase 3 trials will be determined after submission of a detailed protocol. Please also see answer to question #1.

Discussion: ***No discussion.***

Question 3: The proposed Phase 2b clinical study will evaluate patient reported outcomes for cognition, depressed mood, and fatigue. Akebia believes that these endpoints (symptoms) are clinically relevant to the study population and that they should be responsive to treatment with AKB-6548. As such they have been included as secondary outcomes in the Phase 2b protocol for evaluation prior to use in Phase 3 studies.

a) *Does the Agency agree that reductions in cognitive impairment, depressed mood, and fatigue are important markers of treatment benefit in pre-dialysis patients with anemia secondary to CKD?*

b) *Further, does the Agency agree that demonstration of reductions in cognitive impairment, depressed mood, and fatigue versus a placebo comparator during Phase 3 would be appropriate to include in the product label (assuming the outcome of such Phase 3 study assessments are positive)?*

FDA Response: See answer to Question #2.

***Discussion:* No discussion.**

Question 4: To date, the available nonclinical data do not indicate a QT prolongation risk and no evidence of QT prolongation has been observed in Phase 1 or Phase 2 studies. Based upon these data, Akebia is planning to conduct the thorough QTc clinical trial at the beginning of Phase 3 (study design to be submitted at the end of Phase 2).

Does the Division concur with this approach?

FDA Response: Your approach appears to be reasonable. A completed thorough QT study will need to be included in any future NDA submission of AKB-6548. Submit collected human QT data to date along with your thorough QT study clinical protocol for Agency review before initiating the TQT study.

In addition, in your Phase 2b protocol you propose to collect ECG at baseline, week 8 and week 16, however the time points of collection are not provided. We recommend until you get the TQT data to collect ECGs at baseline, at around Tmax (3-4 h) of the parent and the metabolites after first dose and periodically thereafter.

Additional Comments:

1. **Please specify the randomization method (e.g. randomized block) for the study.**
2. **You assume a withdraw rate of 20% in the protocol synopsis, please describe clearly the methods to be used to handle missing data in the protocol.**
3. **Please pre-specify the primary and secondary efficacy analyses in your protocol and provide a detailed statistical analysis plan.**

***Discussion:* No discussion.**

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Not Applicable	FDA	Not Applicable
Not Applicable	Sponsor	Not Applicable

6.0 ATTACHMENTS AND HANDOUTS

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ALBERT B DEISSEROTH
05/21/2012