CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761136Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112562

MEETING MINUTES

Celgene Corporation
Attention: Penny Ng, MSc, MBA RAC
Regulatory Affairs
Corporate Woods, Bldg 32, Suite 900
9225 Indian Creek Parkway,
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Luspatercept (ACE-356).

We also refer to the meeting between representatives of your firm and the FDA on July 29, 2015. The purpose of the meeting was to obtain FDA input on the proposed Phase 3 randomized study design of ACE-536 for the treatment of anemia due to IPSS-R lower to intermediate risk MDS in subjects with ring sideroblasts.

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 me CAPT Diane Hanner, Regulatory Project Manager at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, Ph D, Clinical Team Leader
Division of Hematology Products (DHP)
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: End of Phase 2

Meeting Date and Time: July 29, 2015 @ 3:00 p.m.

Meeting Location: White Oak Campus, Building 22, Room 1313

Application Number: IND 112562

Product Name: Luspatercept (ACE-536)

Indication: The treatment of anemia due to MDS.

Sponsor/Applicant Name: Celgene Corporation

Meeting Chair: Albert Deisseroth, MD, PhD

Meeting Recorder: CAPT Diane Hanner, MPH, MSW

FDA ATTENDEES

- Ann T. Farrell, MD, Division Director , Division of Hematology Products (DHP)
- Albert Deisseroth, MD, PhD, Medical Officer, Clinical Team Leader, DHP
- Avia Krauss, MD, Medical Officer, DHP
- Yun Wang, PhD, Statisitical Reviewer. DB 5
- Lei Nie, PhD, Statistical Team Leader, DB 5
- Olanreqaju Okusanya, Pharm D, Clinical Pharmacology Reviewer, DCP5
- Gene Williams, Pharm D, Clinical Pharmacology Team Leader, DCP5
- Theresa Carioti, MPH., Chief Project Manager (CPMS), DHP
- CAPT Diane Hanner, MPH., MSW, Senior Program Management Officer, DHP

SPONSOR ATTENDEES

- Kenneth Attie, MD, Vice President, Medical Research, Acceleron Pharma
- Jay Backstrom, MD, MPH, Senior Vice President, Global Head Hematology/Oncology Clinical R&D, Regulatory Affairs, Celgene Corporation
- Nianhang Chen, Senior Principal Scientist, Clinical Pharmacology, Celgene Corporation
- James Desiderio, PhD, Vice President, Regulatory Affairs, Acceleron Pharma
- Carolina Giuseppi, MD, Senior Director, Lead Product Safety Physician, Celgene Corporation
- Axel Glasmacher, MD, Corporate Vice President, Clinical Research & Development, Celgene Corporation
- Penny Ng, M.Sc, MBA, RAC, Director, Regulatory Affairs, Celgene Corporation
- Steve Ritland, PhD, MBA, Executive Director, Project Leadership, Celgene Corporation
- Mary Vandekauter, MS, RAC, Director, Regulatory Affairs, Celgene Corporation
- Xianjuan Zhang, Associate Director, Biostatistics, Celgene Corporation
- Xiaosha Zhang, Vice President, Biostatistics, Acceleron Pharma

1.0 BACKGROUND

The Sponsor requested a Type B- IND meeting on May 8, 2015, to discuss the Sponsor's clinical development program for luspatercept for the treatment of anemia due to the revised International Prognostic Scoring System (IPSS-R) very low and low to intermediate risk myelodysplastic syndrome (MDS) patients.

The meeting was granted on May 26, 2015, and was scheduled for July 29, 2015.

2. DISCUSSION

Question 1 - Clinical Development Program:

Does the Agency agree that the proposed clinical development program is adequate to support the registration of luspatercept for the treatment of anemia due to IPSS-R lower to intermediate risk MDS in patients with Ring Sideroblasts?

FDA Response to Question 1 - Dated 23 July 2015:

Please clarify what proportion of MDS patients who are Ring Sideroblast positive, intolerant or un-responsive to ESAs, and who require RBC transfusions, who will be enrolled in the IPSS-R very low, low, and intermediate risk categories respectively in study ACE-536-MDS-001. In order to support the registration of luspatercept for the treatment of anemia due to IPSS-R lower to intermediate risk MDS, you should have a reasonable proportion of patients in each of IPSS-R very low, low and intermediate categories.
If you will use study A536-03 and A536-05 to support the registration of luspatercept, you should analyze the primary efficacy endpoints in these two studies based on the ITT not the EE population.
Please note also that the primary endpoint for study A536-03 was HI-E, an endpoint with which the FDA has not had prior regulatory experience in the approvals of hypomethylating agents for MDS. See also question 7 below.

Celgene Response:

Celgene acknowledges the Agency comments and understands that IPSS-R categories will need to be adequately represented. No further discussion is needed.
Celgene also acknowledges the Agency's comment regarding analysis of the primary efficacy endpoints based on the ITT population for the supporting studies A536-03 and A536-05.

MEETING DISCUSSION to Question 1:

None

Question 2 – Patient Population:

Does the Agency agree with the proposed study design in terms of the definition of the patient population?

FDA Response Dated 23 July 2015:

No. The inclusion criteria define a population of patients who are transfusion dependent, Ring Sideroblast positive, and refractory, intolerant to, or ineligible for ESA treatment. Hypomethylating Agents are approved by the FDA for the treatment of such patients. Therefore, please provide further justification for enrolling this subgroup of IPSS-R very low, low or intermediate risk MDS patients on this trial, instead of treating them first with available approved agents, namely the hypomethylating agents (HMA) azacitibine or decitabine.

Celgene Response:

The intended Phase 3 patient population is defined as lower-risk MDS patients who are transfusion dependent, have ring-sideroblasts and are refractory, intolerant to or ineligible for ESA treatment. Typically, these patients have SF3B1 or other splicing factor mutations, longer survival, and slower progression to AML than other patients with lower risk MDS (Papaemmanuil, 2013; Haferlach, 2014; Malcovati, 2015).
Hypomethylating agents (HMAs), namely azacitidine and decitabine, are approved for lower risk MDS, however these are generally not considered standard of care for lower risk as much as they are for higher risk MDS. In fact, NCCN guidelines recommend the use of HMAs at the same level as lenalidomide and clinical trials for patients with symptomatic anemia with high EPO levels or who are non-responsive to ESAs and have a poor probability to respond to immunosuppressive therapy (IST) (NCCN 2015 guidelines).
Celgene believes that luspatercept should be used ahead of HMAs for patients that are non-responsive to or ineligible for ESAs in order to avoid the risk of Grade 3-4 cytopenias, which occur with both azacitidine and decitabine. Since lower risk MDS patients with ring sideroblasts and low blast counts (<5%) are unlikely to progress to AML, the predominant therapeutic objective is the management of anemia and the prevention of transfusion related complications. Since this might mean 5 or more years of primarily anemia management before disease progression, the benefit/risk of early intervention with HMAs is questionable. For many of these patients, there is a higher risk of cumulative transfusion-related complications than progression to AML. Based on the known mechanism of action, distinct from the EPO receptor pathway, luspatercept acts at the stage of erythropoiesis that is specifically disrupted in RS+ patients. Therefore, Celgene sees a clinical benefit to using a targeted therapy, luspatercept, in the setting of a clinical trial and ahead of HMAs for patients who are non-responsive or ineligible for ESA treatment, consistent with current NCCN treatment guidelines.
The primary endpoint for this study, red blood cell transfusion independence (RBC-TI), is better assessed against the natural history of the disease (ie, in patients previously untreated with disease modifying agents).

MEETING DISCUSSION to Question 2:

The Sponsor clarified that the inclusion criteria, specifically ring sideroblast positive patients with less than 5% marrow blasts, would define a population for which treatment with luspatercept on a clinical trial would be appropriate even without prior HMA therapy. The Agency agreed that this was reasonable in the very low, low, and intermediate risk categories of the IPSS-R.

Question 3 – Stratification Factors:

Does the Agency agree with the proposed stratification factors?

FDA Response Dated 23 July 2015:

Yes, they appear reasonable.

Celgene Response:

No further discussion is needed for this question.

MEETING DISCUSSION to Question 3:

None

Question 4 - Randomization:

Does the Agency agree with the proposed 2:1 randomization?

FDA Response Dated 23 July 2015:

Yes, a 2:1 randomization is reasonable.

Celgene Response:

No further discussion is needed for this question.

MEETING DISCUSSION to Question 4:

None

Question 5 – Control Arm:

Does the Agency agree that placebo is an appropriate comparator?

FDA Response Dated 23 July 2015:

No. If you provide acceptable justification for the inclusion of the proposed patient population in this trial, a more appropriate control arm would be standard of care, e.g. HMAs. Please see questions 1and 2 above.

Celgene Response:

As discussed in the response for Question 2 above, the intended Phase 3 patient population will be patients who are IPSS-R lower risk MDS with ring sideroblasts who are transfusion

dependent and refractory, intolerant to or ineligible for ESA treatment. Since these patients have a particularly low risk of progression to AML and as the management of anemia and the prevention of transfusion-related complications are the predominant therapeutic objectives, a treatment such as HMAs with its risk of grade 3-4 cytopenias should be delayed until the patient progresses to higher risk MDS or has failed more targeted therapy. Therefore the most appropriate comparator would be RBC transfusion ± iron chelation therapy.
Celgene considers luspatercept as a treatment to be used ahead of HMAs to avoid the unnecessary risk of Grade 3-4 cytopenias. In addition, the use of either azacitidine or decitabine (approved HMAs) as a control arm would be very difficult in a blinded study, since both of these HMAs require daily administration for 3–5 days for decitabine or up to 7 days for azacitidine, whereas luspatercept is administered once every 3 weeks. Also given the characteristic adverse event profile for the HMAs (ie, neutropenia, thrombocytopenia, and associated consequences), maintaining the blind would be extremely difficult to conduct.
Celgene therefore proposes retaining placebo as the comparator arm for the Phase 3 study. Standard of care for the management of acute anemia (eg, RBC transfusions) will be applied to both treatment groups during the treatment phase. Subjects will be evaluated for a response after completion of 24 weeks of treatment. Celgene also believes that 6 months of blinded treatment with best supportive care is appropriate and will not pose an undue risk to this slowly progressing patient population, who would still be candidates for subsequent use of HMAs.

MEETING DISCUSSION to Question 5:

The Agency agreed that for the defined patient population above (see question 2) placebo would be an acceptable comparator arm, provided that patients with other cytopenias would be excluded.

Question 6 – Primary Endpoint:

While the sponsor understands that approval will be a review issue, does the Agency agree with the proposed primary endpoint?
FDA Response Dated 23 July 2015:

Your proposal to use the proportion of patients who achieve transfusion independence with a duration of ≥8 week as a primary endpoint is reasonable, but ultimately it will be a review issue.

Celgene Response:

No further discussion is needed for this question.

MEETING DISCUSSION to Question 6:

None

Question 7 – Secondary Endpoints:

Does the Agency agree with the proposed secondary endpoints to support clinical benefit in the target patient population?

FDA Response Dated 23 July 2015:

Your proposal to use the proportion of subjects achieving RBC-TI with a duration of ≥12 weeks as your first key secondary endpoint is reasonable.
Your proposal to use the proportion of subjects achieving HI-E as per IWG 2006 criteria as a second key secondary endpoint is unacceptable, as this is an endpoint with which the FDA has not had prior regulatory experience in the approval of drugs (hypomethylating agents) for MDS. Alternatively, you may wish to use PR or CR, endpoints with which FDA has regulatory experience.

Celgene Response:

Celgene agrees to not use the proportion of subjects achieving HI-E as per IWG 2006 criteria as the second key secondary endpoint (b) (4) but this will be maintained as a secondary endpoint. The first key secondary endpoint will be the proportion of subjects achieving RBC-TI with a duration of ≥12 weeks.
Celgene would like to discuss (b) (4)

Would the Agency provide more information for what would be needed to qualify other secondary endpoints as key secondary endpoint?

MEETING DISCUSSION to Question 7:

None

Question 8 – Statistical Analysis Plan:

Does the Agency agree with the statistical analysis plan for the proposed Phase 3 studies for luspatercept? (Please refer to Appendix 7.3)

FDA Response Dated 23 July 2015:

Please clarify the statistical test you will use for analyzing primary and key secondary efficacy endpoints.

Based on the assumptions you specified, the calculated sample size is ~ 155 not 210 subjects, please explain the discrepancy.

Because you only adjust multiplicity for testing primary and key secondary endpoints, no labeling claim can be made for other secondary endpoints based on comparative analyses.

Celgene Response:

For the primary efficacy endpoint, 56-day RBC transfusion independence, the response rate will be calculated using the number of responders divided by number of subjects in the ITT population (responders plus non-responders). The response rates of the subjects who were randomized to luspatercept and the placebo will be calculated. In the primary efficacy analysis, the statistical hypothesis is

$$H_0 : P_1 = P_2$$
$$H_a : P_1 > P_2$$

where P_1 denotes the true response rate in the luspatercept group, and P_2 denotes the true response rate in the placebo group. The number and percentage of subjects in the ITT population who achieve the response will be presented by treatment group. The Cochran–Mantel–Haenszel (CMH) test will be used to test the difference between the 2 response rates at a 1-sided significance level of 0.025 with randomization factors as strata.

The first key secondary endpoint, proportion of subjects achieving RBC-TI with duration ≥ 12 weeks, will be tested in the same manner as primary efficacy endpoint using the CMH test.

Sample size considerations: The sample size calculation is based on assumption of 90% power for a 30% response rate in the treatment arm and a 10% response rate in the placebo arm, 2:1 randomization and 1-sided alpha 0.025. The z-test with unpooled variance results in n=155 and for pooled variance n=188. The Chi square test also results in a sample size of 188. A slightly lower overall response rate in the luspatercept group due to an estimated 10% dropout rate would result in a sample size of 210.

MEETING DISCUSSION to Question 8:

Your proposal seems acceptable.Please include the details in your study protocol and Statistical Analysis Plan.

Question 9 - Interim Statistical Analysis Plan:

Does the Agency agree with the plan for interim analysis [redacted (b) (4)] *?*

FDA Response Dated 23 July 2015:

No, we have a concern [redacted (b) (4)] Ultimately, this will be a review issue [redacted (b) (4)] We also recommend that you include an interim futility analysis.

Celgene Response:

Celgene acknowledges the Agency's comment and will change the interim analysis to be for futility only. Details will be provided in the SAP. No further discussion is needed on this question.

MEETING DISCUSSION to Question 9:

None

Question 10 - Starting Dose and Dose Titration:

Does the Agency agree with

a) *the proposed starting dose and dosing schedule? and*
b) *the proposed intra-subject dose escalation plan?*

FDA Response Dated 23 July 2015:

Yes.

Celgene Response:

No further discussion of this question is needed.

MEETING DISCUSSION to Question 10:

None

Question 11 - Dose Modification Plan:

Does the Agency agree with the proposed dose reduction modification plan, to manage adverse events (AEs) and excessive hemoglobin increase?

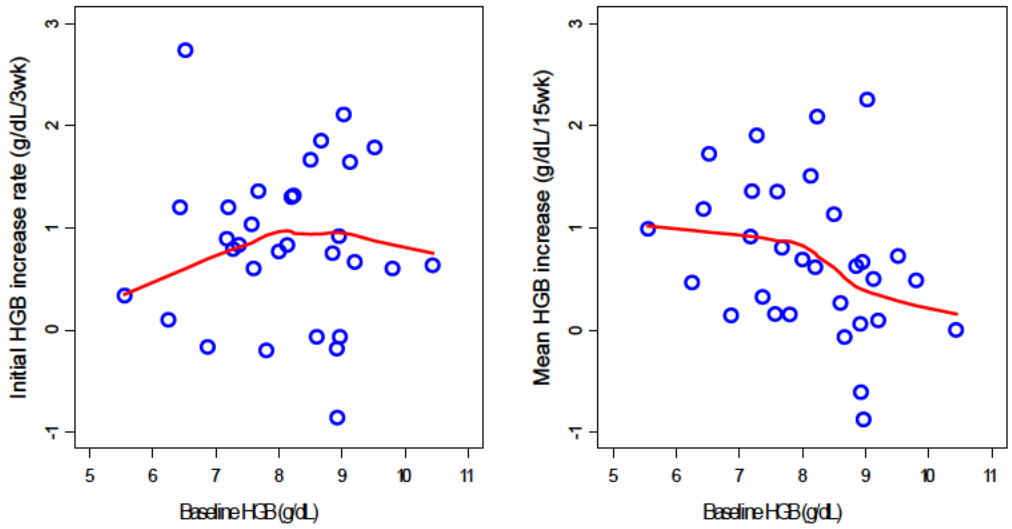
FDA Response Dated 23 July 2015:

No. You have not provided sufficient information showing that a 25% reduction in the dose is adequate to sufficiently slow the rate and extent of hemoglobin change, regardless of the prior rate of change or predose hemoglobin level. Given that you state that the relationship between dose and absolute change in the rate of hemoglobin change is linear, a 25% decrease in dose may still result in ≥ 2.0 g/dL/3 wk. Please provide more information showing the impact of a 25% decrease in dose on the rate of hemoglobin change and the impact of baseline (predose) hemoglobin level on the rate and extent of hemoglobin changes.

Celgene Response:

Celgene would like to note that the relationship between luspatercept dose/exposure and the rate of hemoglobin increase presented in the briefing book was assessed for the first dose (initial rate) using non-transfusion dependent study subjects, where the most rapid hemoglobin increases were observed. In the Phase 2 study, the rate of hemoglobin rise in the transfusion-dependent subjects has been less than in the non-transfusion dependent subjects unless influenced by transfusion.
As of the 07 July 2015 data cutoff date, there were 2 non-transfusion dependent subjects receiving 1.0 and 1.75 mg/kg, respectively, who had a 25% dose reduction due to a hemoglobin increase ≥ 2 g/dL from the previous dosing day. After the 25% dose reduction, the rate of hemoglobin increase did not exceed 2 g/dL in subsequent cycles.
In the Phase 2 study with 58 subjects exposed to luspatercept, there were no transfusion dependent subjects who required dose reduction due to a ≥ 2 g/dL hemoglobin increase from the previous dosing day (ie, 21 days) not attributable to a RBC transfusion. The proposed Phase 3 study will only enroll transfusion dependent MDS subjects.
There was no correlation between baseline hemoglobin and the rate or extent of hemoglobin increase in transfusion dependent subjects who were enrolled in the ongoing Phase 2 study to date (Figure 1).
Based on the above data, Celgene believes a 25% dose reduction is appropriate and adequate to manage acute increases in hemoglobin should they occur in the Phase 3 study.

Figure 1: Relationship between Baseline Hemoglobin and Rate (3 Weeks) or Extent (15 Weeks) of Hemoglobin Change in Transfusion-Dependent Subjects



The symbols are observed data. The red line represents the locally weighted scatterplot smoothing line. All subjects included in the figure were treated at a starting dose of 1 mg/kg. Hemoglobin values within 7 days of transfusion are excluded.

MEETING DISCUSSION to Question 11:

The Agency encouraged the Sponsor to work on the exposure response modeling. Based upon the Sponsor's presentation, the dose modification seems reasonable.

Question 12 - Proposed Long-Term Follow-Up Period for the Phase 3 Study:

Does the Agency agree with the proposed duration of 2 years from the last dose of investigational product for long-term safety follow-up?

FDA Response Dated 23 July 2015:

Yes, this appears reasonable in this patient population.

Celgene Response:

No further discussion of this question is needed.

MEETING DISCUSSION to Question 12:

The Agency and the Sponsor discussed the provisions for long term follow-up of patients receiving luspatercept chronically. The Sponsor offered to introduce provisions for extending the follow-up that is already planned for two years, depending on the outcome of current clinical trials.

Additional comments:

1. In your analysis times section 5.3.4.2.7, you wrote that besides primary analysis, confirmatory analysis will be performed and reported when all subjects have completed 48 weeks of double-blind treatment or have been discontinued from treatment, and a final analysis will be performed and reported when all subjects have been followed for at least 2 years from last dose of study treatment. Please explain how these confirmatory and final analysis results will be used to support your registration.

Celgene Response:

At the time of the BLA submission, the submission package will contain the following data from the Phase 3 study for all patients who have been randomized:

- Primary efficacy analysis at 24 weeks.
- Longer-term efficacy data for up to 48 weeks.
- Long term safety data for at least 48 weeks.

In addition, the BLA will also include long-term safety data from Phase 2 studies in the MDS and β-thalassemia indications. It is anticipated that the safety database will include data available for a total of approximately 287 subjects exposed to luspatercept for up to 27 months at the time of BLA submission for this indication (Table 1).

As noted above, patients will continue to be followed for up to 2 years for long-term safety (progression to AML and survival) from the last dose of investigational product in the Phase 3 study.

Table 1: Estimated Safety Database for the Luspatercept Clinical Development Program for MDS

	Luspatercept	Placebo	Total
Phase 1 Studies	**24**	**8**	**32**
Multi-dose (A536-02)	24	8	32
Phase 2 Studies	**123**	**0**	**123**
A536-03/05 MDS Study	58	--	58
A536-04/06 β-Thal Study	65	--	65
Phase 3 Study	**140**	**70**	**210**
Phase 3 Study in MDS	140	70	210
All Clinical Studies	**287**	**8**	**295**
Healthy Volunteers	24	8	32
MDS	198	--	198
β-Thalassemia	65	--	65

*Does the Agency agree that a single, well-controlled, randomized study will support the registration of luspatercept in this indicatio**n?***

MEETING DISCUSSION to Additional Comment 1:

None

2. In your rationale for question 6, you wrote "A comparison of the proportion of subjects achieving RBC-TI with a duration ≥ 8 weeks at 24 weeks with that at 48 weeks will be performed (included as secondary endpoint) to ensure the continuation of the treatment effect." However, in your study protocol synopsis, -the proportion of subjects achieving RBC-TI with a duration ≥ 8 weeks at 48 weeks was not listed as one of the secondary endpoints. Please clarify.

Celgene Response:

Celgene intends to have as a secondary endpoint the proportion of subjects achieving RBC-TI with a duration ≥ 8 weeks from randomization to 48 weeks. This will be included in the final protocol submission. No further discussion is needed at this meeting.

MEETING DISCUSSION to Additional Comment 2:

The adequacy of a single adequate well controlled trial supported by additional data for a regulatory decision will be a review issue.

REFERENCES (AVAILABLE UPON REQUEST)

Haferlach T, Negata Y, et al. Landscape of Genetic Lesions in 944 Patients with Myelodysplastic Syndromes. Leukemia 2014; 2014 Feb;28(2):241-7.

Malcovati L, Karimi M, et al. SF3B1 Mutation Identifies a Distinct Subset of Myelodysplastic Syndrome with Ring Sideroblasts. Blood 2015 Jul 9;126(2):233-41.

NCCN Clinical Practice guidelines in Oncology (NCCN guidelines) Myelodysplastic syndromes version I.2016, published on 28 May 2015.

Papaemmanuil E, Gertsung, M, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 2013; 122 (22):3616-3627.

3.0 IMPORTANT MEETING 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.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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

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 CDER/CBER Position on Use of SI Units for Lab Tests (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.

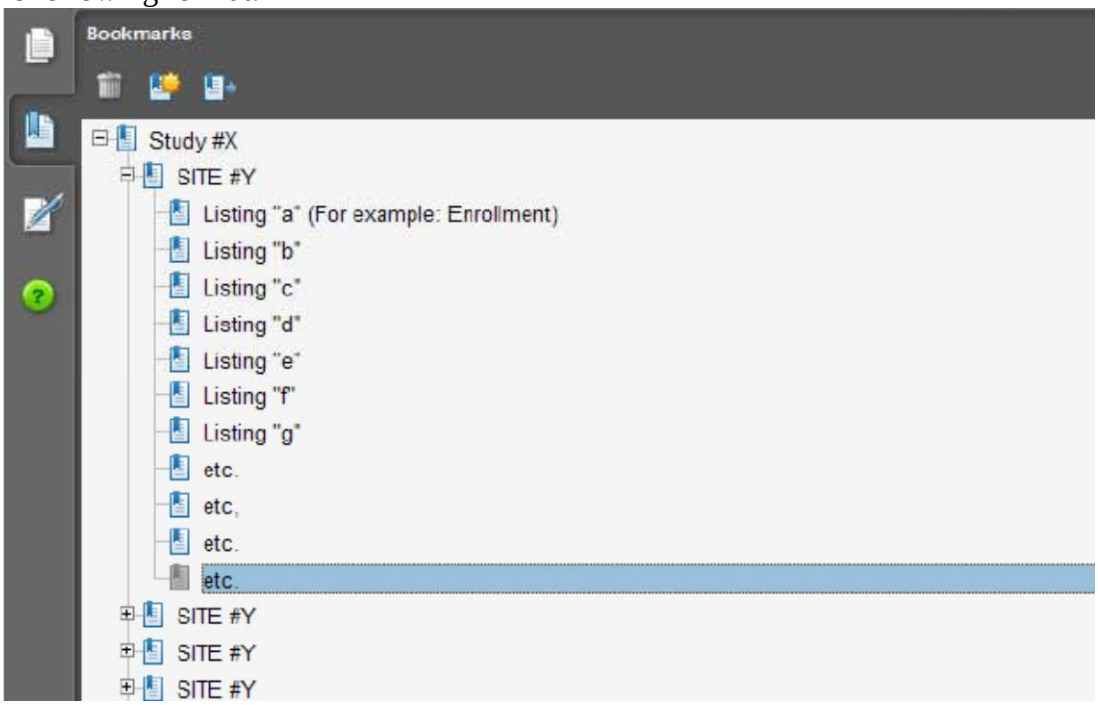
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No additional issues requiring further discussion were identified.

5.0 ACTION ITEMS

No additional action items were identify during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

No additional attachments or handouts were distributed for inclusion in the meeting minutes.

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

/s/

ALBERT B DEISSEROTH
08/07/2015