CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761197Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 113552

MEETING MINUTES

Genentech, Inc.
Attention: Meike Lorenz-Candlin, PhD
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Lorenz-Candlin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Port Delivery System with Ranibizumab (PDS).

We also refer to the teleconference between representatives of your firm and the FDA on August 17, 2020. The purpose of the meeting was to discuss the Study GR40548 and to review the registration strategy to form the basis of a BLA submission. A copy of the official minutes of the meeting/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 Lois Almoza, M.S., Senior Regulatory Health Project Manager at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: August 17, 2020 from 2:00pm – 3:00pm (EST)
Meeting Location: Teleconference

Application Number: 113552
Product Name: Port Delivery System with Ranibizumab (PDS)
Indication: Neovascular (wet) Age-Related Macular Degeneration
Sponsor Name: Genentech, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Lois Almoza, MS

FDA ATTENDEES

Wiley Chambers, MD, Acting Director, Division of Ophthalmology (DO)
William Boyd, MD, Clinical Team Leader, DO
Martin Nevitt, MD, Clinical Reviewer, DO
Sonal Wadhwa, MD Clinical Reviewer, DO
David Summer, MD, Clinical Reviewer, DO
Shilpa Rose, MD, Clinical Reviewer, DO
Rhea Lloyd, MD, Clinical Reviewer, DO
Guoxing Soon, PhD, Biostatistics Team Leader, Division of Biometrics IV (DBIV)
Yunfan Deng, PhD, Biostatistics Reviewer, DBIV
Amy Hsu, PhD, Product Reviewer, Office of Biotechnology Products (OBP)
Kristen Nickens, PhD, Product Quality Team Leader, (OBP)
Ingrid Chapman, PharmD, BCPS, Senior Risk Management Analyst, Division of Risk Management, (DRM)
Nasim Roosta, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Oyinlola Fashina, PhD, General Health Scientist, DMEPA
Lois Almoza, MS, Senior Regulatory Health Project Manager, Division of Regulatory Operations for Specialty Medicine

SPONSOR ATTENDEES

Giulio Barteselli, M.D. Medical Director, Clinical Science, Ophthalmology
Chris Brittain, Global Head Ophthalmology, Product Development,
Meleeneh DerHartunian, Ph.D., Principal Regulatory Documentation Scientist, Product Development, Regulatory
Erica Evans, Ph.D. Group Director, Product Development, Regulatory

Anne Fung, M.D. Global Development Lead, Clinical Science, Ophthalmology
Lori Grace, B.S. Program Director, Pharma Technical Regulatory
Derrick Kaufman, Ph.D. Principal Statistical Scientist, Biostatistics
Pascal Guibord, M.Sc. Associate Director, Biostatistics
Meike Lorenz-Candlin, Ph.D., Program Director, Product Development, Regulatory
Katie Maass, Ph.D. Scientist, Clinical Pharmacology, Pharmacology Subteam Leader
Shrirang Ranade, Ph.D. Technical Development Team Leader, Pharma Technical Development
Philip Risser, B.A. Global Regulatory Franchise Head, Ophthalmology
Natasha Singh, Pharm.D. Principle Director, Clinical Safety
Erica Vonasek, Ph.D Program Manager, Product Development, Regulatory
Jeff Willis, M.D., Ph.D Medical Director, Clinical Science, Ophthalmology

BACKGROUND

The proposed to be marketed dosage form of the PDS will be a (b) (4) which contains 100 mg/mL ranibizumab formulation, the proposed to be marketed dosing regimen for patients with nAMD consists of an initial fill of the PDS implant and surgical insertion of the filled PDS implant into the patient's eye, followed by refills of the PDS implant (100 mg/mL formulation) Q24W.

DISCUSSION

Following, in **bold** font, are the questions in the July 16, 2020, Meeting Package. The FDA response to these questions are in *italic* font. Meeting Discussions that took place during the August 17, 2020, teleconference are in regular font.

CLINICAL/STATISTICAL/SAFETY

1. **Does the Agency agree that the totality of the available data from Study GR40548, supported by Studies GX28228 and GR40549, provide a favorable benefit-risk profile and sufficient clinical evidence of effectiveness to support the review of the BLA for patients with nAMD?**

   FDA Response: Decisions about approvability of a BLA can only be made once a complete BLA is submitted and reviewed. Studies GR40548, GR40549 and GX28228 alone are unlikely to be sufficient to support the approval of the application. Reliance on adequate and well controlled trials demonstrating the safety and efficacy of ranibizumab is also likely to be necessary.

Meeting Discussion: Genentech asked for further clarification regarding the PDS clinical data to be included in the BLA and the comment that these data alone are unlikely to be

sufficient to support approval. The Agency noted that if these studies had not used ranibizumab but had used a new molecular entity (NME), they would not be sufficient to support a BLA. The knowledge about the ranibizumab molecule comes from the BLA for Lucentis (ranibizumab injection). Since the Sponsor has right of reference to this information, the expectation is it will be used to fill in any missing information for a new BLA. The Agency confirmed that cross-referencing is acceptable.

Genentech plans to support the Clinical and Clinical Pharmacology with cross references as appropriate to the Lucentis BLA; the Agency noted that this was acceptable.

The Agency could not provide additional comments on assessment of the benefit-risk profile for the PDS in nAMD since this determination requires full review of the study reports.

2. **Does the Agency agree that the totality of the available data from Studies GR40548, GX28228, and GR40549 support a proposed PDS 100 mg/mL Q24W treatment regimen?**

   FDA Response: *See response to Question #1.*

Meeting Discussion: The Agency confirmed no additional analysis are expected to be needed to inform the treatment regimen, but the full PDS data set is expected in order to allow further assessment by the Agency. The Agency agreed relevant legacy information from the Lucentis BLA could be formally included using cross-references. Although the Agency has not identified any particular concerns to date, the Agency could not comment on whether the proposed regimen is an appropriate regimen until the BLA is submitted and full study reports have been reviewed.

3. **Does the Agency agree with the proposed benefit-risk analysis approach based on the totality of the available data from Study GR40548, including:**
   a. **Methodology**

      FDA Response: *No.*

Meeting Discussion: Genentech asked the Agency to comment about specific items on the proposed list of variables for the planned benefit-risk analysis. The Agency clarified it considers the change in Best Corrected Visual Acuity (BCVA) and the gain or loss of 15 letters from baseline to be clinically significant. Other elements, such as (b) (4) , are not considered clinically significant.

(b) (4)

. The Agency disagreed with the proposed benefits and considered the outlined list of adverse events incomplete. In addition, the proposed framework did not establish weights for each element and the Agency did not consider each element to be of equal weight.

The Agency commented that for the risk assessment, all adverse events need to be considered. Genentech clarified that in evaluating the safety profile, all adverse events would be considered. However, the risks included in the B/R assessment were those the team deemed as clinically important.

b. Variables chosen to be included in analysis

FDA Response: *No. The proposed benefits include multiple items which are not necessarily clinical benefits. The proposed risks do not include all potential risks.*

(b) (4)

Meeting Discussion: None

c. (b) (4)

FDA Response: *Disagree.*

Meeting Discussion: None

4. **Does the Agency agree with the:**
   a. **Sponsor's assessment that the impact of COVID-19 on the primary analysis is low**

      FDA Response: *Determination can only be made once a complete BLA is submitted and reviewed.*

Meeting Discussion: None

   b. **Sponsor's proposed plan for summarizing the potential impact of COVID-19 on the safety data in the BLA?**

      FDA Response: *Your assessment appears reasonable. Determination can only be made once a complete BLA is submitted and reviewed.*

Meeting Discussion: None

MULTI-DISCIPLINARY

5. **In light of the results from Studies GR40548, GR40549, and GX28228 and the planned risk management strategy, including routine labeling, does the Agency agree with the Sponsor's position that a risk evaluation and mitigation strategy (REMS) proposal will not be required for inclusion in the PDS BLA for the proposed indication?**

   FDA Response: *Decisions about REMS proposal of a BLA can only be made once a complete BLA is submitted and reviewed.*

Meeting Discussion: The Agency noted that there were not any risks that had been identified to date that would warrant a REMS. The Agency noted that the closest precedents in ophthalmology risk to the proposed product were glaucoma filtering procedures and devices. Circumventing the eye's natural biological barriers represented

a potential risk. This potential risk for patients receiving the PDS was considered a topic to be addressed in the BLA submission and review.

6. **Does the Agency agree with the plans outlined to provide a PDS-specific periodic benefit-risk evaluation report (PBRER), separate from Lucentis, based on PDS postmarketing experience?**

   FDA Response: Decisions about PBRER of a BLA can only be made once a complete BLA is submitted and reviewed.

Meeting Discussion: Genentech restated they would like to provide separate PBRERs for the PDS and Lucentis. The Agency noted that the PBRER contents would need to describe two different sets of data with portions that are overlapping. As long as each PBRER was complete, the Agency did not object to two separate PBRERs.

ADMINISTRATIVE/REGULATORY

7. **Does the Agency agree that the results from Study GR40548, supported by Studies GX28228 and GR40549 are adequate to support a safety and effectiveness claim for the following proposed indication?**

   Tradename is indicated for the treatment of adult patients with neovascular age-related macular degeneration.

   FDA Response: See response to Question #1.

Meeting Discussion: None

8. **Does the Agency agree that the results represent a significant advancement in the treatment of patients with nAMD in order to qualify the proposed BLA for Priority Review?**

   FDA Response: No. A demonstration of non-inferiority over an approved product does not demonstrate a significant advancement. Any potential improvement in safety would have to be demonstrated in the safety data set and not just be a theoretical improvement in safety. Decisions regarding priority review are made once a BLA is submitted.

Meeting Discussion: The Agency confirmed that without a clinical demonstration of superiority in safety or efficacy, the application was unlikely to receive a Priority Review (PR). The Agency referred to the guidance documents that describe the need to demonstrate that there is a benefit over current therapies. There are multiple products approved and available for the proposed indication. The Agency confirmed upon a

concluding question by Genentech that, based on information available so far, the proposed BLA is unlikely to be granted PR based on the merits of the clinical data.

Genentech then explored whether, in the event a Priority Review voucher is used for the planned BLA, a request for a rolling submission (RS) is possible based on Fast Track designation in nAMD for the PDS. The Agency agreed that, while granting of a RS request is not guaranteed, the Agency is open to the proposal, and if sought, would likely agree to it. Genentech also outlined the current timelines with eCTD Module 3 content available by end of March 2021, but clinical and nonclinical data likely being ready for submission at an earlier date, such as December 2020. Genentech inquired about how useful such a RS would be deemed by the Agency. The Agency noted that a RS based on early submission of nonclinical and clinical data is unlikely to speed up review of the application since the rate limiting step tends to be the CMC package and completion of the GMP inspections. Submitting CMC information early would be more likely helpful and an action on a BLA can only be taken once review of all parts has been completed.

9. **Based on the preliminary review of the data, does the Agency foresee that the proposed BLA will be reviewed by an Advisory Committee?**

   FDA Response: A determination will be made following submission of a complete BLA and filing review.

Meeting Discussion: The Agency reiterated that a determination of whether an Advisory Committee (AC) meeting is needed will occur following the submission of a complete BLA. While the molecular entity is not new, the delivery method is unlike typical ophthalmic delivery systems. It is not clear at this time, if the new delivery method would benefit from public discussion prior to approval.

10. **Does the Agency have any other comments or recommendations regarding the proposed BLA content or its preparation?**

    FDA Response: No additional comments.

Meeting Discussion: None

Additional Meeting Discussion: Regarding review by CDRH of the implant, Genentech inquired whether the Agency could provide further insight in how the CDER reviewers plan to interact with the CDRH team, especially considering the implant. The Agency noted that CDER considers the implant to be a dispenser and is therefore regulated as a drug and not a medical device. CDER would do the primary review of the implant and while reviewers can call on other Agency resources when needed, it was expected that

drug standards, not medical device standards would be applied. However, the ancillary devices would be within the scope of CDRH review.

In discussion on facility inspections, the Agency noted that facility inspections would be based on drug cGMPs similar to other ophthalmic dispensers such as eye droppers or drop bottles. Genentech pointed out that the implant and devices are manufactured and packaged in their own sterile-barrier system and carton. There is no drug in the manufacture or packaging of the implant and other devices. They are manufactured at a medical device manufacturer that is compliant to the 21 CFR 820 QSR. Based on the cGMPs for Combination Products, Genentech anticipated that the company would be inspected per device manufacture regulations as there is no drug involved in the manufacturing and drug GMPs are not applied. Genentech proposed to pursue this topic further in future meetings.

(b) (4)

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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
- 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

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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/

WILEY A CHAMBERS
09/16/2020 09:51:32 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113552

MEETING MINUTES

Genentech, Inc.
Attention: Meike Lorenz-Candlin, PhD
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Lorenz-Candlin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ranibizumab Port Delivery System (RPDS). We also refer to the Type-B, End of Phase 2 Meeting between representatives of your firm and the FDA on March 23, 2018.

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 Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date/Time: March 23, 2018, 10:00 am

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Meeting Type: Type-B, End of Phase 2

Application: IND 113552

Drug Name: Ranibizumab Port Delivery System (RPDS)

Sponsor: Genentech, Inc.

Meeting Chair: Wiley Chambers
Meeting Recorder: Michael Puglisi

FDA PARTICIPANTS: Division of Transplant and Ophthalmology Products
Wiley Chambers/ Supervisory Medical Officer
Peter Stein/ Deputy Director, Office of New Drugs
William Boyd/ Clinical Team Leader
Sonal Wadhwa/ Clinical Reviewer
Rhea Lloyd/ Clinical Reviewer
Martin Nevitt/ Clinical Reviewer
Philip Colangelo/ Clinical Pharmacology Team Leader
Yunfan Deng/ Statistics Reviewer
Yan Wang/ Statistics Team Leader
Maria Rivera/ Nonclinical Reviewer
Nasim Roosta/ Division of Medication Error Prevention and Analysis
Millie Shah/ Division of Medication Error Prevention and Analysis
Michael Puglisi/ Regulatory Project Manager

SPONSOR PARTICIPANTS: Genentech, Inc.
Bonaventure Agata/ Lucentis Life Cycle Leader
Vladimir Bantseev/ Scientist/Toxicologist, Safety Assessment
Giulio Barteselli/ Associate Medical Director, Clinical Science Ophthalmology
Christopher Brittain/ Senior Medical Director, Clinical Science Ophthalmology
Ronald Cantrell/ Principal Real World Data Scientist
Jason Ehrlich/ Global Head, Clinical Ophthalmology, Product Development, Clinical Science

Erica Evans/ Senior Regulatory Leader, Regulatory Affairs
Lori Grace/ Program Director, Pharma Technical Regulatory
William Hanley/ Global Development Team Leader
David Kardatzke/ Project Lead Statistician, Biostatistics
Meike Lorenz-Candlin/ U.S. Regulatory Partner, Regulatory Affairs
Katie Maass/ Clinical Pharmacology Leader, Clinical Pharmacology; Pharmacology Subteam Leader
Matthew Meldorf/ Global Franchise Head, Ophthalmology and New Diseases I2ON, Regulatory Affairs
Shrirang Ranade/ Technical Development Team Leader
Natasha Singh/ Senior Director Safety Science, Safety Risk Management
Fan Tang/ Statistician, Biostatistics
(b) (4)

MEETING OBJECTIVE:
The purpose of this meeting was to discuss Phase 3 development plans for the Ranibizumab Port Delivery System (RPDS) for treatment of wet AMD.

SUMMARY OF DISCUSSION:
Agency responses to the questions outlined in the February 1, 2018, background package (see bolded text below) were provided to the Sponsor in an email dated March 19, 2018 (see text in italics below). This meeting served to clarify those responses. Discussion during the meeting is reflected in normal font. The Sponsor's slide presentation is attached at the end of this document.

QUESTIONS FOR DISCUSSION:

CLINICAL/STATISTICAL
Question 1a
Does the Agency agree with the target patient population, which will include patients with nAMD diagnosed within (b) (4) months prior to the screening visit, and responsive to anti-VEGF intravitreal injections within 6 months prior to the screening visit?

Agency Response: No, while 9 months prior to the screening visit is acceptable, it would be preferable to limit the study population to having a diagnosis of nAMD within 6 months or less to better align with the studies establishing the non-inferiority margin.

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 1b
(b) (4)

Agency Response: No. The primary endpoint of change in BCVA from baseline should be at least 9 months after the treatment period. It would be acceptable to average over Weeks 36, 40 and 44. We will need to review the protocol and statistical analysis plan.

Meeting Discussion:
There was a discussion concerning the potential acceptability of a single equivalence study to support the BLA submission. The Agency confirmed that a single equivalence trial is acceptable in some cases, but there is not enough data to conclude that at this time and the Agency recommends two adequate and well controlled studies. The equivalence margin for these trials is recommended to be no more than 4.5 letters for the upper or lower margins. For trials with a primary endpoint of change in BCVA from baseline, the Agency agreed that the first timepoint could be an average of Weeks 36 and 40.

[redacted] (b) (4)

The Agency agreed to review and comment upon a draft study protocol and draft statistical analysis plan, if submitted. The timeframe for such a review is unclear, however, if submitted as a Special Protocol Assessment, the timeframe for a response would be 45 days.

Question 1c
Does the Agency agree that ranibizumab administered via Q4W intravitreal injections is an appropriate comparator?

Agency Response: *Yes, we agree that ranibizumab Q4 weeks is an acceptable comparator.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 1d
Does the Agency agree with the proposed non-inferiority margin of 4.5 letters?

Agency Response: *Yes, we agree.*

Meeting Discussion: Please refer to discussion for Question 1b.

Question 1e
Does the Agency agree with the proposed Phase III dose and dosing regimen?

Agency Response: *The proposed dosing regimen appears acceptable.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 1f
Does the Agency agree with the proposed ranibizumab intravitreal injection rescue strategy for patients whose disease activity is not sufficiently controlled with fixed-interval RPDS refills?

Agency Response: *Using Q4 weeks ranibizumab as a rescue treatment through week 96 is acceptable.*

Meeting Discussion:
Regarding rescue thereapy, Regeneron clarified that a single intravitreal ranibizumab injection will be administered to patients when they meet protocol-defined rescue criteria. Genentech proposed allowing rescue intravitreal ranibizumab only at Weeks 16 and/or 20 following the initial fill or any subsequent refill. Patients would continue to receive implant refills as per the protocol (i.e., at Weeks 24, 48, 72, and 96 post-randomization) and will not be discontinued from the study treatment.

Regarding classification as a treatment failure requiring rescue therapy, the Agency disagree with a number of the proposed definitions, but agreed that a reduction of 15 letters or more compared to the best BCVA would be a treatment failure. The Agency stated that, to the extent possible, it would like patients to be followed throughout the trial. It recommended performing multiple types of analyses.

The Agency stated that the primary analysis should include consideration of patients who receive rescue therapy that may impact the efficacy outcomes. The Agency also recommended that the reasons for rescue therapy administration be collected in the case report forms. The Agency's proposed trimming approach was discussed. There was disagreement concerning whether the trimming approach would provide analysis which was potentially biased against the study drug.

The Agency stated that it is potentially acceptable to use masked data to revise or finalize the primary statistical analysis. The Agency agreed to consider specific proposals in regard to statistical analyses.

Question 1g
Does the Agency agree with the proposed plans for PK and ADA analysis?

Agency Response: Your proposal for the PK and ADA analyses are generally acceptable. However, we have the following comments:

- *Upon submission of the complete study protocol, please provide the number of patients that you plan to assess the pharmacokinetics of ranibizumab in the (b) (4) mg/mL RPDS ((b) (4) mg) treatment arm and in the 0.5 mg IVT administration treatment arm.*
- *We recommend that you add an additional ADA sampling timepoint at Week 4. All scheduled ADA sampling timepoints are to coincide with that of the PK sampling timepoints.*
- *We note that PK comparison between the (b) (4) mg/mL RPDS ((b) (4) mg) treatment and the 0.5 mg IVT treatment needs to include an evaluation of the C_{max} of ranibizumab from the respective treatments. Therefore, we recommend that you employ adequate PK sampling timepoints to capture the C_{max}.*

Meeting Discussion:
Regarding ADA sampling, the Agency reiterated its recommendation to add an additional ADA sampling timepoint at Week 4, as it believes sampling at Week 4 is just as informative as at later timepoints.

Regarding the number of patients for PK, the Sposnor indicated that they intend to assess PK for the RPDS and the ranibizumab IVT injection cohorts in all patients enriolled in the trial (approx. 117 in each treatment arm). The Agency stated that for PK, it is not necessary to assess PK in all patients, but rather, assessment from a subset of patients from each treatment arm is sufficient; that is, a minimum of 10 PK-evaluable patients per treatment arm is acceptable.

Regarding evaluation of Cmax for RPDS and IVT ranibizumab, the Agency acknowledged that the systemic PK of Lucentis following IVT administration has been adequately characterized in previous clinical studies, therefore, full characterization of the PK of Lucentis by IVT administration is not neeeded in the proposed study with the RPDS. However, the Agency further explained that evaluation of ranibizumab Cmax within the same study for both routes of administration would provide a more direct evaluation, as opposed to comparing Cmax across different studies. The Agency also stated that assessment of Cmax following the IVT administration of Lucentis in the proposed RPDS trial is not a requirement, and would depend upon if patient visits afford the opportunity for a Cmax sample. The Sponsor indicated that they will attempt to evaluate Cmax following IVT injection of Lucentis in the proposed RPDS trial.

Question 1h
Does the Agency agree with the proposed Phase III safety monitoring plan?

Agency Response: *Yes.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 1i
Does the Agency agree with the plan for statistical analysis of the primary endpoint, including the imputation methods?

Agency Response: No. (b) (4) *We recommend you consider the trimmed mean approach (https://www.ncbi.nlm.nih.gov/pubmed/27523396) for patients who receive rescue therapy and patients who discontinue the study treatment due to adverse events in the primary analysis. Your proposed analysis can be conducted as supplementary analysis.*

Additionally, we recommend you take measures to follow and conduct efficacy and safety evaluation for all treated patients throughout the study regardless of the occurrences of the intercurrent events that may impact the treatment effect of the study product. You should collect detailed information on the reasons of discontinuation for early study dropouts.

Meeting Discussion: Please refer to discussion for Question 1b and 1f.

Question 1j
Can the Agency comment on (b) (4)

(b) (4)
?

Agency Response: *See response to Question #1b.*

Meeting Discussion: Please refer to discussion for Question 1b.

Question 1k
Can the Agency comment on the approvability of change in BCVA from baseline at Week 36 as an alternative primary endpoint?

Agency Response: *Yes, we agree.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 1l
Taking into consideration the design elements of the proposed Phase III Study GR40548, the existence of substantive effectiveness data for ranibizumab intravitreal injection in nAMD, and supportive data for the RPDS program from the Phase II Study GX28228, does the Agency agree that a single non-inferiority study could support a BLA for the RPDS?

Agency Response: *No, we do not agree. The Agency expects two adequate, well-controlled trials to demonstrate safety and efficacy.*

A protocol synopsis has been submitted; the Agency may have additional comments once the final protocol is submitted.

Meeting Discussion:
Regarding the Agency's expectation for two adequate, well-controlled trials, Genentech proposed performing one non-inferiority trial in the AMD indication (b) (4)

(b) (4)

Question 2
Does the Agency have any comments regarding the design and objectives of the proposed extension Study GR40549?

Agency Response: *A protocol synopsis has been submitted, the Agency may have additional comments once the final protocol is submitted.*

Meeting Discussion: Please refer to discussion for Question 1b.

Question 3
Does the Agency agree that the proposed number of patients and patient exposure in the safety database will support a BLA for the RPDS in nAMD?

Agency Response: It is recommended that the clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. To accomplish this, it is recommended that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. Prior to an NDA submission, it is recommended that at least 300 patients would have completed at least 12 months of follow-up after the initiation of treatment.

Meeting Discussion:
Regarding the safety database, Regeneron proposed that for both the Phase 3 and the extension portion, at least 300 patients would have completed at least 12 months of follow-up after the initiation of treatment. The Agency agreed this is acceptable and stated that the safety database can be pooled (b) (4).

NONCLINICAL
Question 4
Does the Agency agree that the completed nonclinical program satisfies all necessary requirements and that no additional studies, beyond the planned biocompatibility studies, are required to support the following?

- **The proposed RPDS Phase III program**
- **Submission of a BLA for the RPDS**

Agency Response: Based on the information provided in the briefing document, we agree no additional nonclinical studies are required to support the Phase 3 program or BLA submission. However, the adequacy of these studies to support approval will be a review issue.

For any of the components which travel through interstate commerce with the ranibizumab, we do not anticipate that any ISO testing will be required for our review.

Meeting Discussion: There was no discussion of this matter during the meeting.

ADMINISTRATIVE/REGULATORY
Question 5
Does the Agency agree that a clinical data submission package inclusive of the following would be sufficient to support a BLA for the RPDS?

- **Pivotal data from the proposed single Phase III Study GR40548**
- **Supportive data from the Phase II Study GX28228**
- **Supportive data from the proposed extension Study GR40549**
- **Supportive safety data from the Phase I Study FH-1.2**

Agency Response: *We cannot determine whether there is sufficient information to support a BLA without reviewing the study results of GX28228 and GR40548.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 6
Does the Agency agree that the planned clinical data submission package outlined in Question 5 supports the following proposed indication statement?

The RPDS is indicated for patients with nAMD.

Agency Response: *Labeling is a review issue and can only be determined once a complete BLA package is submitted. However, the target patient population of patients with neovascular AMD appears acceptable.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 7
Regarding the Phase III Study GR40548 design, can the Agency comment on the potential labeling implications, if any, of pre-treatment with intravitreal anti-VEGF therapy?

Agency Response: *As mentioned previously, labeling is a review issue. However, if patients have been screened based on their response to anti-VEGF therapy and received a loading dose in the trials, you should expect the label to contain such a description.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 8
Based on the design of the proposed Phase III Study GR40548, the Sponsor anticipates that initial approval will be based on a fixed dosing regimen of Q24W. Can the Agency comment on their expectations for data that could support (b) (4) **?**

Agency Response: *Labeling is a review issue and can only be determined once a complete BLA package is submitted. Data to support* (b) (4) *. A protocol synopsis has been submitted; the Agency may have additional comments once the final protocol and statistical analysis plan are submitted.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 9
Does the Agency agree that the totality of the proposed clinical program based on the

Phase III Study GR40548 in nAMD would allow [redacted] (b) (4) **?**

Agency Response: *No,* [redacted] (b) (4) .

Meeting Discussion: Please refer to discussion for Questions 1b and 11.

Question 10
Does the Agency have any other comments on the proposed clinical development program for this novel intraocular drug delivery system?

Agency Response: *No additional comments.*

Meeting Discussion: There was no discussion of this matter during the meeting.

Question 11
Does the Agency agree that the interim data from the Phase II Study GX28228 demonstrates the potential for [redacted] (b) (4)

Agency Response: No, [redacted] (b) (4)

[redacted] (b) (4)

Meeting Discussion:
Genentech confirmed that no components of the RPDS will be marketed independent of ranibizumab. The Agency stated that pursuant to 21 CFR 200.50, the delivery system is regulated as a drug and may be submitted as a stand-alone BLA. The Agency reiterated that should Genentech plan on marketing components without the ranibizumab, the Center for Devices and Radiologic Health (CDRH) should be contacted about pre-marketing requirements for the particular device components which will be marketed without ranibizumab.

Additional Agency Comments:

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 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 Pedsdrugs@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*

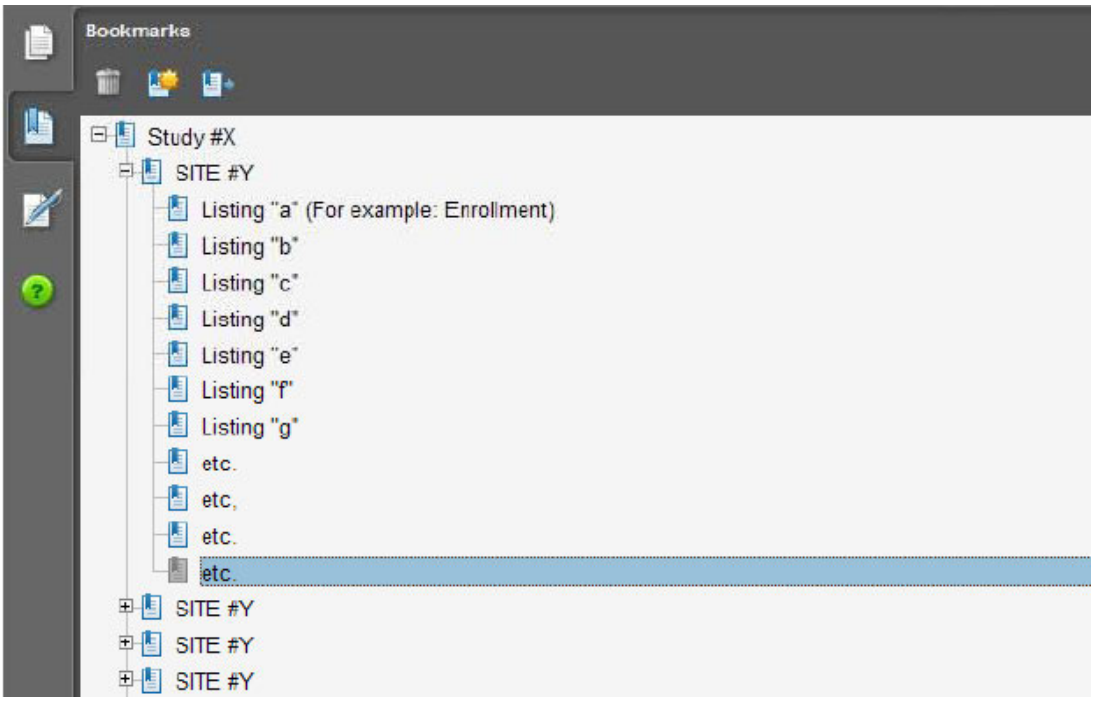
b. *Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, 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.*

[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

Meeting Discussion: There was no discussion of the Additional Agency Comments during the meeting.

ACTION ITEM:
The Agency agreed to provide minutes of the meeting within 30 days.

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

/s/

WILEY A CHAMBERS
04/08/2018