CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761235Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 119225

MEETING REQUEST CANCELLED

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
Attention: Jay Bordoloi, Pharm.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Bordoloi:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for faricimab (RO6867461). We also refer to your March 25, 2021, communication requesting cancellation of the Pre-BLA meeting we scheduled for March 29, 2021, in response to your January 11, 2021, meeting request. The meeting was cancelled because the Meeting Preliminary Comments provided by the Agency on March 22, 2021, "were clear and no further discussion was needed," as stated in a March 25, 2021, email to Dr. Wendy Streight from Dr. Jay Bordoli, Regulatory Program Manager from Genentech.

Because the application that was 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, the pre-submission meeting was intended to include discussion and 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. At the meeting, you and FDA might have also reached 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.

We note that you have not proposed late submission of minor application components. Therefore, your application is expected to be complete at the time of original submission.

If you have any questions, please call me at 240-402-6498.

Sincerely,

{See appended electronic signature page}

Wendy Streight, PhD
Regulatory Health Project Manager
Ophthalmology
Division of Regulatory Operations for Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

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

/s/

WENDY M STREIGHT
03/30/2021 01:23:55 PM

IND 119225

MEETING PRELIMINARY COMMENTS

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
Attention: Jay Bordoloi, Pharm.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Bordoloi:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for faricimab (RO6867461). We also refer to your January 11, 2021, correspondence, requesting a meeting to discuss your anticipated BLA submission.

Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. The official record of this meeting will be the FDA-generated minutes. If you have any questions, please call me at 240-402-6498.

Sincerely,

{See appended electronic signature page}

Wendy Streight, PhD
Regulatory Health Project Manager
Ophthalmology
Division of Regulatory Operations for Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date: March 29, 2021
Meeting Time: 12:00 PM – 1:00 PM

Application Number: 119225
Product Name: faricimab (RO6867461)

Indication: Neovascular Age-Related Macular Degeneration
Diabetic Macular Edema
Diabetic Retinopathy

Sponsor Name: Hoffmann-La Roche/Genentech, Inc.
Regulatory Pathway: 351(a)of the Public Health Service Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 29, 2021, between Hoffmann-La Roche (Roche) and the Division of Ophthalmology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

DISCUSSION
Following, in **bold**, are the questions submitted in the February 23, 2021, meeting package. The FDA responses to these questions are in *italics*.

CLINICAL

1. **Does the Agency agree that efficacy and safety results from the outlined studies support the submission of a marketing application for the intended indications?**

   FDA response: The clinical studies, TENAYA, LUCERNE, YOSEMITE and RHINE are adequate to support the filing of a BLA for faricimab to treat nAMD

and DME. However, the adequacy of the study results to support approval is a review issue.

(b) (4)

REGULATORY

2. **Does the Agency expect to convene an Advisory Committee for this BLA application?**

   FDA response:
   The decision as to whether the Agency would convene an Advisory Committee meeting is made after the filing of the BLA/NDA.

3. **Does the Agency agree with the proposed potential submission plan, pending the final size of the BLA?**

   FDA response: The Agency has no objection to submitting the BLA via the eCTD gateway as multiple submissions. The PDUFA clock would start when the complete BLA submission has been received by the Agency.

CHEMISTRY, MANUFACTURING, AND CONTROLS

4. **With the uncertainty associated with COVID-19 restrictions for travel and on-site inspection, the marketing authorization holder (MAH) will make all possible efforts to support alternative inspection approaches. Can the FDA provide additional considerations on the pre-license inspection (PLI) approach and timing? Would the FDA also be open to discuss alternative options with the MAH in case pandemic-related restrictions inhibit the ability of the Agency to inspect the site in accordance with PDUFA timelines?**

FDA response: *It is premature to discuss alternative inspection approaches for the application until the application has been submitted. The Agency must assess the ability of the manufacturing facilities to conduct the listed manufacturing operations in compliance with cGMP. Under normal circumstances, the proposed manufacturing schedule appears reasonable, assuming the BLA is submitted in May 2021. However, given the current public health situation, as well as travel restrictions, the Agency is unable to determine whether inspection of the facilities can be conducted prior to the User Fee Date. For more information, please refer to FDA guidance related to COVID-19. Guidance can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.*

ADDITIONAL AGENCY COMMENTS

Regarding Product Quality:

1. To facilitate the Agency's review of the drug substance and drug product manufacturing process for faricimab, provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Process parameter/ operating parameter/ in-process control (IPC)	Proposed Range for Commercial Manufacturing	Criticality classification[1]	Range assessed during process development studies	Validated Range	Clinical Study Range	Justification of the proposed commercial acceptable range[2]

[1]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[2]Provide a brief summary description (e.g., "development range", "validation range", or "platform experience"). To link to additional description for justification you may additionally include a link or reference to the appropriate section of the eCTD with more detail.

2. To facilitate the Agency's review of the control strategy for faricimab, provide information for quality attributes and process and product related impurities for the drug substance and drug product in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3. Attributes that are deemed to not be critical should also be justified in the BLA with the reasoning for that categorization.

Critical Quality attributes (including Process and Product related impurities for DS and DP)	Impact[1]	Source[2]	Analytical method[3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]

[1]What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.
[2]What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein purification column.
[3]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[4]List all the ways the attribute is controlled, e.g., in-process testing, validated removal, release testing, stability testing.
[5]Provide a brief verbal description. In addition, you may provide links or references to appropriate sections of the eCTD that provide more detail.

3. To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications of faricimab DS and DP, provide information for each release specification in the tabular format provided below. Please provide a separate table for faricimab DS and DP, as described below. Each release specification should be described in a separate row. Add additional rows for additional release specifications, as needed. In general, include footnotes for each column of grouped results to indicate which lot numbers were used for each calculation of minimum-maximum range, and provide the correct number (n=?) in the table also. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do not replace other

parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Release Specification for Faricimab Drug Substance							
Attribute	Analytical Method	Proposed Commercial Release acceptance criteria	Release results for developmental batches (n=?) (min-max)	Release results for DS batches[a] (n=?) used in clinical studies (min-max)	Release results for DS PPQ batches (n=?) (min-max)	Release results for all batches[b] made using commercial process (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

a. Include batches of different scales if he batch was used in any clinical testing. List each of he batch numbers included as footnote in the table.

b. Include all batches with available release data that were manufactured following he proposed commercial process, included those prior to PPQ campaign. Include a list of the batch numbers included in analysis as a footnote in he table.

Release Specification for Faricimab Drug Product							
Attribute	Analytical Method	Proposed Commercial Release acceptance criteria	Release results for nonclinical and developmental DP batches (n=?) (min-max)	Release results for clinical DP batches[a] (n=?) (min-max)	Release results for DP PPQ batches (n=?) (min-max)	Release results for all batches[b] made using commercial process (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

a. Include all batches used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List each of the batch numbers included as footnote in the table.

b. Include all batches with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.

4. To facilitate the Agency's assessment of the adequacy of the stability specifications of faricimab DS and DP, provide stability information for storage at recommended condition for each stability specification in the tabular format provided below. Please provide a separate table for faricimab DS and DP, as

described below. Each stability specification should be described in a separate row. Add additional rows for additional stability specifications, as needed. If any stability specifications are different than the corresponding release specification for an analytical method that is used for both, then provide justification why different acceptance criteria are proposed for release and stability. Include footnotes to the tables to list the batch numbers that were used in each assessment. Consider the data from all stability time points, not only release and end of proposed shelf-life. If a lot has not completed stability testing to the end of the proposed shelf-life, include data from all time points that are currently available for that lot in the evaluation. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Stability Specification for Faricimab Drug Substance				
Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at recommended condition (n=?) [a] Min – Max (Range for all data from time 0 to the proposed end of shelf life or currently available)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

a. Include a list of the batch numbers that were used in each assessment.

Stability Specification for Faricimab Drug Product				
Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at at recommended condition (n=?) [a] Min – Max (Range for all data from time 0 to the proposed end of shelf life or currently available)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

a. Include a list of the batch numbers that were used in each assessment.

5. To facilitate the Agency's assessment of the suitability of the analytical methods for release and stability testing of DS and DP and for in-process test methods,

provide summarized results of method validation in the tabular format provided below. Please provide a separate table for each analytical method, as described below. Each parameter, e.g. specificity, precision, accuracy, etc. should be described in a separate row. Add additional rows for additional parameters, as needed. Study design should include a brief description of the testing material (batch information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used such as DS release/stability, DP release/stability, or in-process testing.

Summary of Validation Results for XXX (Method) (Used for DS release/stability, in-process testing, etc.)			
Location of testing site:		**Location where method was validated:**	
System Suitability Acceptance Criteria:			
Parameter	**Study Design**	**Acceptance Criteria**	**Validation Results**
a. Provide a reference to supporting information and data in he BLA for method transfer, as applicable, for methods hat were validated in a different place than where they will be tested for commercial QC testing.			

6. Provide the following information in a completed table like the one below for all drug master files referenced in your biologics license application:

DMF #	DMF Type	DMF Holder	Item referenced	Link to Letter of Authorization	Comments (if needed)

Regarding Immunogenicity:

7. Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports on Biopharmaceutical Studies and 5.3.5 Reports of Efficacy and Safety Studies. For the BLA file we recommend that the applicant provide the Integrated Summary of Immunogenicity (ISI) in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:

a) Immunogenicity Risk Assessment- this section should provide a concise immunogenicity risk assessment specific to the therapeutic product, in accordance to the principles discussed in the FDA Guidance (2014*) Immunogenicity Assessment for Therapeutic Protein Product.* This section

should include discussions on product quality -related factors and how these may impact the immunogenic potential of the product; patient- related factors including a discussion on how likely is the patient population and clinical indication to result in immunogenic responses to the product, and a section on trial design-related factors, with a discussion of how the clinical study conditions may facilitate an immunogenic response to the product.

b) Tiered strategy and Stage-Appropriate Bioanalytical Assays- This section should provide details on the tiered immunogenicity strategy that applicant followed in the clinical program, and validation summaries for the various immunogenicity assay methods that were developed throughout the program. In addition, this section should provide links to method development and validation reports for all the immunogenicity assays used in the various clinical studies supporting the application, particularly those used to test immunogenicity samples from the pivotal clinical study(ies).
c) Clinical Study Design and Sampling Strategy: this section should provide the immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed. This section should include as justification for pre-treatment, in-treatment, and post-treatment sampling time points for immunogenicity and pharmacokinetics, where applicable. This section should discuss how the immunogenicity program aims to reveal the incidence, persistence and clinical significance of anti-drug antibodies.
d) Clinical Immunogenicity Data Analysis- This section should provide summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of linear and/or non-linear correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data. This section should include drug levels measured in the samples tested for anti-drug antibodies, and trace drug product batches used in the individual clinical studies. Discussion should examine the impact of any pre-existing antibodies on pharmacokinetics, safety and efficacy, the impact of treatment-emergent anti-drug antibodies on pharmacokinetics, pharmacodynamics, efficacy and safety.

Regarding Microbiology:

Please consider the following comments during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

8. All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

9. The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

    - Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
    - Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
    - Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
    - Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
    - Information and summary results from the shipping validation studies (3.2.S.2.5).
    - Drug substance bioburden and endotoxin release specifications (3.2.S.4).
    - Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

10. The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

11. The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

    - Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

12. The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies.
- Validation of capping parameters, using a container closure integrity test.

13. The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity

testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 21, 2021, 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. 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]

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

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] 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 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.

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[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for

[4] https://www.fda.gov/media/84223/download

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

commercial production and those used for product and manufacturing process development.

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*.[6]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar

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

biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

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/

WENDY M STREIGHT
03/22/2021 07:47:09 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119225

MEETING MINUTES

Hoffman-La Roche Inc.
Attention: Jay Bordoloi, Pharm.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Bordoloi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO6867461. We also refer to the meeting between representatives of your firm and the FDA on August 30, 2018. The purpose of the meeting was to discuss the development of RO6867461 for the treatment of DME and nAMD.

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. We also include a copy of the Meeting Minutes (Attachment 2) captured live, as part of a pilot program in the Division.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial 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: EOP2

Meeting Date and Time: August 30, 2018, from 12:30 PM to 1:30 PM
Meeting Location: Building 22, Room 1311

Application Number: 119225
Product Name: RO6867461
Indication: treatment of neovascular age-related macular degeneration and diabetic macular edema
Sponsor Name: Hoffman-La Roche Inc.

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Diana Willard

FDA ATTENDEES

Wiley Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, M.D.	Clinical Team Leader, DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Abhay Joshi, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Solomon Chefo, Ph.D.	Statistical Reviewer, OB/DBIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Zhenzhen Liu, Ph.D.	Product Quality Reviewer, Office of Pharmaceutical Quality/Office of Biotechnology Products /Division of Biotechnology Review and Research III
Judit Milstein, M.S.	Chief, Project Management Staff, DTOP
June Germain	Regulatory Project Manager, DTOP
Wendy Streight, Ph.D.	Regulatory Project Manager, DTOP
Diana Willard	Chief, Project Management Staff, DTOP

HOFFMAN LA ROCHE ATTENDEES

Francis Abreu Cedeno, Ph.D.	Statistician, Biostatistics
Karen Basu, Ph.D.	Project Lead Statistician, Biostatistics
Jay Bordoloi, Pharm.D.	Regulatory Partner, Regulatory Affairs
Tim Burkoth, Ph.D.	Global Regulatory Leader, Regulatory Affairs
Nilesh Mehta	Life Cycle Leader, Global Product Strategy
Jason Ehrlich, M.D., Ph.D.	Global Head, Clinical Ophthalmology, Product Development Clinical Science
Virginie Garlet, Pharm.D.	Regulatory Partner, Regulatory Affairs
Hugh Lin, M.D.	Clinical Science Leader, Clinical Ophthalmology
Aaron Osborne, M.D.	Global Development Team Leader, Clinical Ophthalmology
David Silverman, M.Sc., M.B.Ch.B., MRCOpth, FFPM	Clinical Science, Clinical Ophthalmology

BACKGROUND

A June 6, 2018, Meeting Request from Hoffman La Roche (Roche) requested a meeting to share data from the Phase 2 nAMD studies (BP29647 [AVENUE] and CR39521 [STAIRWAY]), to provide a draft Phase 3 nAMD protocol (design to be finalized after global EoP2 health authority interactions) for discussion and to confirm the anticipated registration plans for the treatment of both DME and nAMD. A June 11, 2018, Meeting Request Granted letter listed August 30, 2018, as the agreed upon meeting date.

The Meeting Package was received on June 20, 2018. FDA sent Preliminary Comments to Roche on August 23, 2018. In an e-mail dated August 27, 2018, Roche indicated that they would, "... would like to discuss question 3 and 6 face-to-face." In an e-mail dated August 29, 2018, Roche provided visual aids to facilitate the meeting discussion (Attachment 1).

DISCUSSION

Following, in **bold font**, are the questions in the June 20, 2018, Meeting Package. The FDA's August 23, 2018, responses to these questions are in *italic* font, the August 27, 2018, responses from Roche are in ***bold italic*** font, and meeting discussion is in regular font.

Pharmacology/Toxicology

1. Toxicology Program for DME and nAMD

Does the Agency agree:

- **that the completed nonclinical program to support the DME Phase 3 clinical program also supports the nAMD Phase 3 clinical program, with no further studies needed prior to initiation of the nAMD Phase III studies?**

- **with the design of the proposed developmental toxicity assessment study that will be included in the BLA, and that no further nonclinical studies will be needed for the planned DME and nAMD BLA?**

FDA Response: We concur with your approach. Adequacy of the data will be a review issue. Please see the minutes of the April 24, 2018, type B meeting regarding the nonclinical information requested for the BLA. Regarding the design of the monkey embryofetal study, please consider the following:

a. *You proposed 4 weekly iv injections, to cover the period of organogenesis (gestation days 20-50). We recommend 5 weekly doses (e.g. GD20, 27, 34, 41, 48).*
b. *We generally recommend 16-22 per group. You have proposed groups of 16 pregnant female cynomolgus monkeys/dose, and we have no objection. Please be aware that this group size might not be adequate, depending on postimplantation loss. Please consider the laboratory's recent historical control data, for the design of the study.*
c. *Provide TK data (e.g., maternal; placental and/or amniotic/fetal at C-section).*

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback and will incorporate the recommended changes to the study. No further discussion is needed.

Clinical/Statistical

2. Phase 3 Study Design

Does the Agency agree that the proposed Phase 3 pivotal study design would be sufficient to support a BLA for the indication of treatment of patients with nAMD? In particular, does the Agency agree with the:

a) Study population?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

b) Dose and treatment regimens for RO6867461 and aflibercept active comparator arm?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

c) Timing of disease activity assessment at Week 20 and Week 24 in Arm A RO6867461 to determine dosing intervals ranging between every 8 weeks (Q8W) and Q16W up to the primary endpoint?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

d) Definition and timing of the primary endpoint?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

e) Proposed analysis plan?

FDA Response: Your proposed analysis plan appears acceptable on the condition that the number of subjects who receive prohibited therapy or discontinue the study drug due to lack of efficacy or adverse events in both treatment groups is small. The final dosing regimen that will be included in the labeling is a review issue.

Additional Comment :

*We recommend that 'lack of efficacy' be included in the case report form as one of the reasons for early withdrawal. Also, in Section 4.6.2 (Patient Discontinuation from Study) of the protocol, you included the following categories as reasons for early withdrawal: '**Investigator or Sponsor determines it is in the best interest of the patient**' or '**Patient non-compliance**', but these categories seem to be general descriptors for early withdrawal. Thus, we recommend that you collect more detailed reasons for these categories and make every effort to determine whether subjects discontinue the study due to an adverse event or lack of efficacy or both.*

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback, and will make the recommended changes to the case report form. No further discussion is needed.

3. Phase 3 Design Beyond Week 48

Does the Agency agree that the below options for the design of the study beyond Week 48 support the ability to add Year 2 data to product labeling via the registration plans outlined in Question 6?

a) No change to Year 1 treatment regimen in the second year

FDA Response: Yes. Provided masking and efficacy are maintained through to the end of the two-year study, the pertinent 2-year data may be reflected in the labeling.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

b) An additional disease activity assessment beyond Week 48

FDA Response: Yes. Provided masking and efficacy are maintained through to the end of the two-year study, the pertinent 2-year data may be reflected in the labeling. It is unlikely that the specific disease activity assessment would be included in the labeling unless the specific criteria have been shown to be predictive of clinical outcomes.

Roche August 27, 2018, response: The Sponsor would like to discuss this topic to better understand the Agency's perspective. A visual aid will be provided to facilitate discussion during the 30 August 2018 meeting.

Meeting Discussion: Roche stated that under the current proposal, some investigators have expressed concern that select patients may not be treated optimally or may drop out. Roche proposed a possible option to address this issue with a single assessment timepoint at week 60 in the second year. A decision would be made at that assessment timepoint whether to change treatment.

The Agency stated their belief that the appropriate tools to optimize dosing of any VEGF products do not currently exist. To date, the labeling has identified a recommended dose and identified dosing regimens which have been shown to be inferior. The Agency continues to recommend that multiple parameters be collected.

The Agency believes that patients can tell when they have been administered a sham injection. Although information regarding data from year 2 might be used in the labeling for this product, it will most likely be safety information. At this point in time without having the data, it is unknown what (if anything) will be stated in the labeling regarding efficacy. (b) (4)

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c) Treat and extend

FDA Response: Unlikely, however, a final determination will be made after review of the data.

Roche August 27, 2018, response: The Sponsor would like to discuss this topic to better understand the Agency's perspective. A visual aid will be provided to facilitate discussion during the 30 August 2018 meeting.

Meeting Discussion: The Agency stated that it can be difficult to interpret different dosing regimens administered to the same patient over the course of the study, making labeling more challenging. From a safety perspective, the Agency stated that labeling may include a range of doses. For efficacy, most likely what will be included in the labeling would be the dose regimen that provides the best visual acuity.

d) Rescue therapy utilizing the assigned study treatment

FDA Response: A determination will be made after review of the data dependent on whether the information is necessary for the safe and effective use of the product.

Roche August 27, 2018, response: The Sponsor would like to discuss this topic to better understand the Agency's perspective. A visual aid will be provided to facilitate discussion during the 30 August 2018 meeting.

Meeting Discussion: The Agency stated that depending on how often rescue therapy is needed a determination will be made whether to include this information in the labeling.

4. Safety Monitoring Plan

Does the Agency agree with the proposed key aspects of the safety monitoring plan for the Phase 3 nAMD studies?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

5. Safety Database

Does the Agency agree that the proposed number of patients and patient exposure in the safety database will support a BLA submission and potential approval for RO6867461 in nAMD?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

Regulatory

6. Biologics License Application Submission Plans

Does the Agency agree full approval for RO6867461 would be appropriate to pursue via the following BLA submission plan:

a) A single original BLA for the treatment of DME and nAMD (1 year), followed by submission of 2-year DME and nAMD data during review of the original BLA (depending on final 2-year data availability)?

FDA Response: No. Except for the 4-month safety update, the application is expected to be complete at the time of the filing of the BLA. Additional efficacy data during the review of the application can be submitted as a new BLA submission.

Roche August 27, 2018, response: The Sponsor would like to clarify the submission plans for the BLA containing data from both the DME and nAMD indications and understand the Agencies guidance.

Reference is made to below nAMD EoP2 Question 8 and to FDA's feedback to the DME EoP2 question 11a on the 24 April 2018 DME EoP2 meeting minutes (copied below).

> ***24 April 2018 DME EoP2 Meeting Minutes dated 21 May 2018:***
> ***Question 11. Biologics License Application Submission Plans***
> ***Does the Agency agree full approval for RO6867461 would be appropriate to pursue via the following BLA submission options:***
> ***a) A single original BLA for the treatment of DME (1 year), followed by submission of 2 year DME data during review of the original BLA (depending on final 2-year data availability)***

FDA Response: We agree.

Meeting Discussion: The Agency clarified that BLAs need to be complete at the time of submission. If Roche wants to submit more data for a new claim BEFORE the Agency takes an action on the first application, they can do this via a new BLA, but Roche will need to pay a new User Fee. The difference between the question that was asked for the April 24, 2018, meeting and this meeting is that now the issue of a new claim has been introduced.

b) Following submission and review of final 2-year DME and nAMD data during the original BLA review, approval and labeling of 2-year data for DME and nAMD with the initial approval?

FDA Response: See Response to Question 6a.

Roche August 27, 2018, response: See Response to Question 6a for proposed discussion on this topic.

Meeting Discussion: See Meeting Discussion for Question 6a.

7. <u>Alternative Development Plan with Single Pivotal Study Registration</u>

In the context of the recently available nAMD data from two Phase 2 studies (AVENUE and STAIRWAY), does the Agency agree that a single positive Phase 3 nAMD study combined with the Phase 2 data could be sufficient to support submission of a BLA?

FDA Response: The Agency will need to review the final study report from both studies before answering this question. Based on the information provided in the meeting package, AVENUE does not appear to have sufficient efficacy data and STAIRWAY does not have sufficient study patients to be fully supportive of an application.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

8. <u>Alternative Development Plan with 1 Year Studies</u>

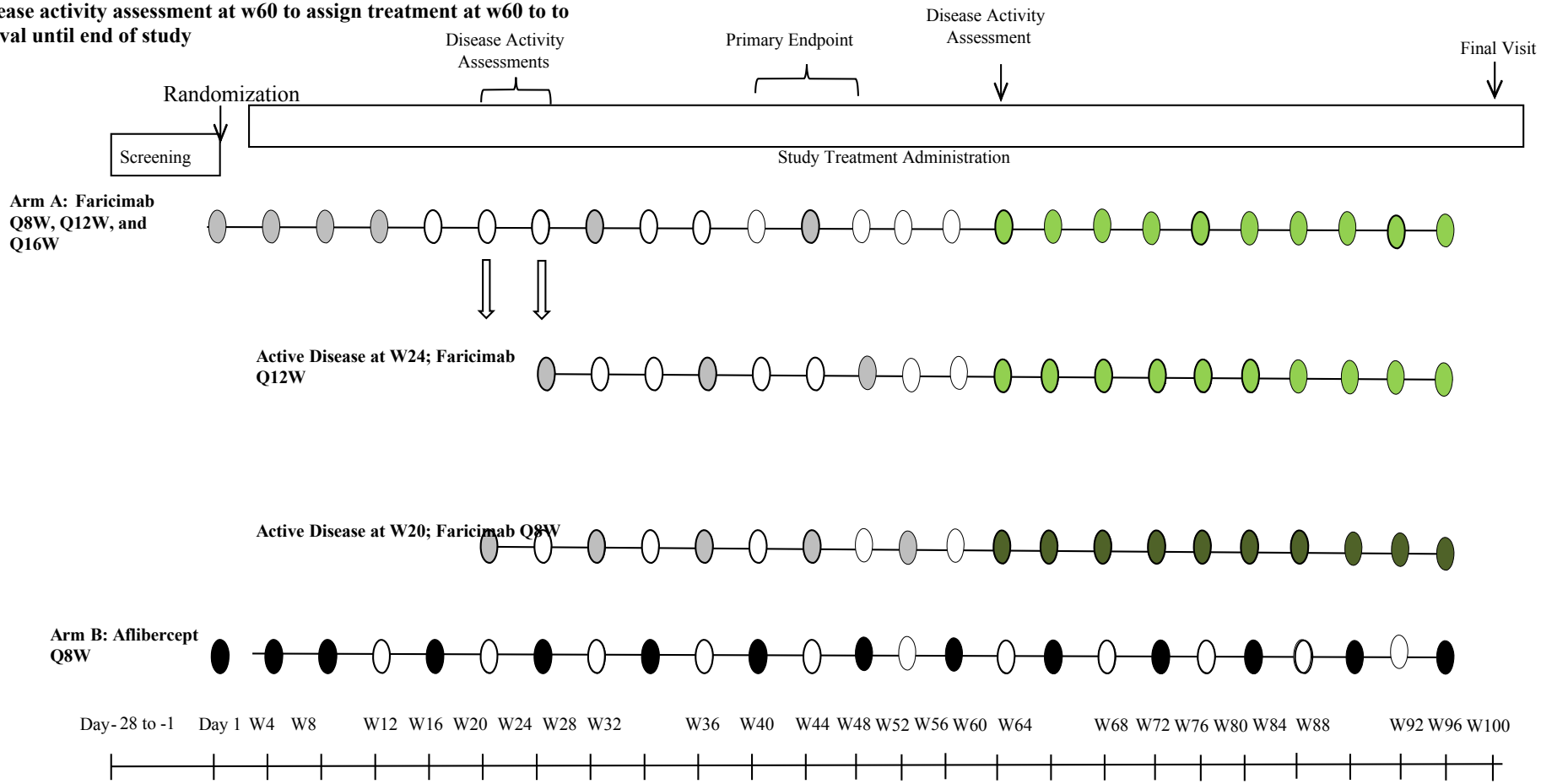
In the context of collecting long term data via eventual open label extension studies for both nAMD and DME, does the Agency agree that stopping the study at the primary analysis (Weeks 40 through 48) could also support submission of a BLA?

FDA Response: Yes, for the nAMD indication. The open label extension data would be considered supportive safety data. No, for the DME indication. The Agency expects the BLA to be supported by 1 year or longer efficacy data. The Agency expects a BLA to be supported by at least 2 years of safety data.

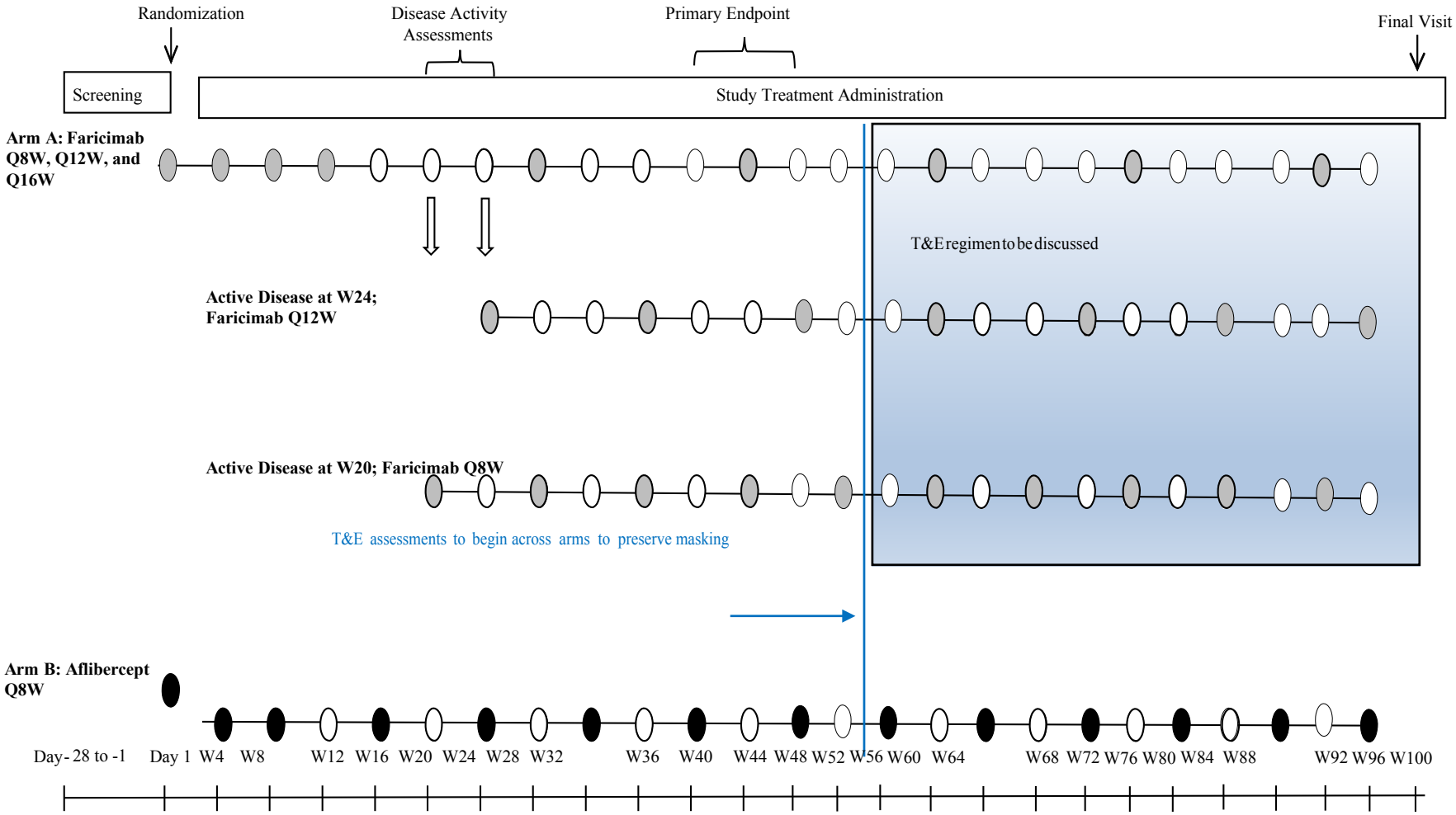
Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. We would like to discuss the BLA submission plans as part of Question 6.

APPEARS THIS WAY ON ORIGINAL

Phase III Year 2: Disease activity assessment at w60 to assign treatment at w60 to to assign treatment interval until end of study



Phase III Year 2: Treat and Extend (T&E)



Attachment 2

Live Minutes of the Meeting

Following, in **bold font**, are the questions in the June 20, 2018, Meeting Package. The FDA responses to these questions are in *italic* font, the August 27, 2018, responses from Roche are in ***bold italic*** font, and meeting discussion is in regular font.

Pharmacology/Toxicology

1. Toxicology Program for DME and nAMD

Does the Agency agree:

- **that the completed nonclinical program to support the DME Phase 3 clinical program also supports the nAMD Phase 3 clinical program, with no further studies needed prior to initiation of the nAMD Phase III studies?**
- **with the design of the proposed developmental toxicity assessment study that will be included in the BLA, and that no further nonclinical studies will be needed for the planned DME and nAMD BLA?**

FDA Response: We concur with your approach. Adequacy of the data will be a review issue. Please see the minutes of the April 24, 2018, type B meeting regarding the nonclinical information requested for the BLA. Regarding the design of the monkey embryofetal study, please consider the following:

a. *You proposed 4 weekly iv injections, to cover the period of organogenesis (gestation days 20-50). We recommend 5 weekly doses (e.g. GD20, 27, 34, 41, 48).*
b. *We generally recommend 16-22 per group. You have proposed groups of 16 pregnant female cynomolgus monkeys/dose, and we have no objection. Please be aware that this group size might not be adequate, depending on postimplantation loss. Please consider the laboratory's recent historical control data, for the design of the study.*
c. *Provide TK data (e.g., maternal; placental and/or amniotic/fetal at C-section).*

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback and will incorporate the recommended changes to the study. No further discussion is needed.

Clinical/Statistical

2. Phase 3 Study Design

Does the Agency agree that the proposed Phase 3 pivotal study design would be sufficient to support a BLA for the indication of treatment of patients with nAMD? In particular, does the Agency agree with the:

a) Study population?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

b) Dose and treatment regimens for RO6867461 and aflibercept active comparator arm?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

c) Timing of disease activity assessment at Week 20 and Week 24 in Arm A RO6867461 to determine dosing intervals ranging between every 8 weeks (Q8W) and Q16W up to the primary endpoint?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

d) Definition and timing of the primary endpoint?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

e) Proposed analysis plan?

FDA Response: Your proposed analysis plan appears acceptable on the condition that the number of subjects who receive prohibited therapy or discontinue the study drug due to lack of efficacy or adverse events in both treatment groups is small. The final dosing regimen that will be included in the labeling is a review issue.

Additional Comment :

*We recommend that 'lack of efficacy' be included in the case report form as one of the reasons for early withdrawal. Also, in Section 4.6.2 (Patient Discontinuation from Study) of the protocol, you included the following categories as reasons for early withdrawal: '**Investigator or Sponsor determines it is in the best interest of the patient**' or '**Patient non-compliance**', but these categories seem to be general descriptors for early withdrawal. Thus, we recommend that you collect more detailed reasons for these categories and make every effort to determine whether subjects discontinue the study due to an adverse event or lack of efficacy or both.*

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback, and will make the recommended changes to the case report form. No further discussion is needed.

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Does the Agency agree that the below options for the design of the study beyond Week 48 support the ability to add Year 2 data to product labeling via the registration plans outlined in Question 6?

a) No change to Year 1 treatment regimen in the second year

FDA Response: Yes. Provided masking and efficacy are maintained through to the end of the two-year study, the pertinent 2-year data may be reflected in the labeling.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

b) An additional disease activity assessment beyond Week 48

FDA Response: Yes. Provided masking and efficacy are maintained through to the end of the two-year study, the pertinent 2-year data may be reflected in the labeling. It is unlikely that the specific disease activity assessment would be included in the labeling unless the specific criteria have been shown to be predictive of clinical outcomes.

Roche August 27, 2018, response: The Sponsor would like to discuss this topic to better understand the Agency's perspective. A visual aid will be provided to facilitate discussion during the 30 August 2018 meeting.

Meeting Discussion: The Division responded that the current tools available are insufficient to determine the best timeframe to administer anti-VEGF medications, and the results will need to be reviewed prior to making a decision on labeling. The results from year 1 and year 2 will define the efficacy that is captured in the final labeling. There is no direct correlation between visual acuity and optical coherence tomography (OCT).

c) Treat and extend

FDA Response: Unlikely, however, a final determination will be made after review of the data.

Roche August 27, 2018, response: The Sponsor would like to discuss this topic to better understand the Agency's perspective. A visual aid will be provided to facilitate discussion during the 30 August 2018 meeting.

Meeting Discussion: The Division responded that multiple assessments involved in treat and extend increases variability within patients and between investigators, and makes it more difficult to analyze; therefore, it is less likely to be included in the labeling.

d) Rescue therapy utilizing the assigned study treatment

FDA Response: A determination will be made after review of the data dependent on whether the information is necessary for the safe and effective use of the product.

Roche August 27, 2018, response: The Sponsor would like to discuss this topic to better understand the Agency's perspective. A visual aid will be provided to facilitate discussion during the 30 August 2018 meeting.

Meeting Discussion: The Division responded that depending on how often rescue therapy occurs will determine whether it will be included in labeling.

4. Safety Monitoring Plan

Does the Agency agree with the proposed key aspects of the safety monitoring plan for the Phase 3 nAMD studies?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

5. Safety Database

Does the Agency agree that the proposed number of patients and patient exposure in the safety database will support a BLA submission and potential approval for RO6867461 in nAMD?

FDA Response: Yes.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

Regulatory

6. Biologics License Application Submission Plans

Does the Agency agree full approval for RO6867461 would be appropriate to pursue via the following BLA submission plan:

a) A single original BLA for the treatment of DME and nAMD (1 year), followed by submission of 2-year DME and nAMD data during review of the original BLA (depending on final 2-year data availability)?

FDA Response: No. Except for the 4-month safety update, the application is expected to be complete at the time of the filing of the BLA. Additional efficacy data during the review of the application can be submitted as a new BLA submission.

Roche August 27, 2018, response: The Sponsor would like to clarify the submission plans for the BLA containing data from both the DME and nAMD indications and understand the Agencies guidance.

Reference is made to below nAMD EoP2 Question 8 and to FDA's feedback to the DME EoP2 question 11a on the 24 April 2018 DME EoP2 meeting minutes (copied below).

24 April 2018 DME EoP2 Meeting Minutes dated 21 May 2018:
Question 11. Biologics License Application Submission Plans
Does the Agency agree full approval for RO6867461 would be appropriate to pursue via the following BLA submission options:

a) A single original BLA for the treatment of DME (1 year), followed by submission of 2 year DME data during review of the original BLA (depending on final 2-year data availability)

FDA Response: We agree.

Meeting Discussion: The Division responded that an original application may have multiple indications and pay only one user fee, and a supplemental application may have only one indication. However, if submitting a second indication or additional claim as an amendment during the original review cycle, then it will require a new BLA application and another user fee.

b) Following submission and review of final 2-year DME and nAMD data during the original BLA review, approval and labeling of 2-year data for DME and nAMD with the initial approval?

FDA Response: See Response to Question 6a.

Roche August 27, 2018, response: See Response to Question 6a for proposed discussion on this topic.

Meeting Discussion: See Meeting Discussion for Question 6a.

7. <u>Alternative Development Plan with Single Pivotal Study Registration</u>

In the context of the recently available nAMD data from two Phase 2 studies (AVENUE and STAIRWAY), does the Agency agree that a single positive Phase 3 nAMD study combined with the Phase 2 data could be sufficient to support submission of a BLA?

FDA Response: The Agency will need to review the final study report from both studies before answering this question. Based on the information provided in the meeting package, AVENUE does not appear to have sufficient efficacy data and STAIRWAY does not have sufficient study patients to be fully supportive of an application.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

8. <u>Alternative Development Plan with 1 Year Studies</u>

In the context of collecting long term data via eventual open label extension studies for both nAMD and DME, does the Agency agree that stopping the study at the primary analysis (Weeks 40 through 48) could also support submission of a BLA?

FDA Response: Yes, for the nAMD indication. The open label extension data would be considered supportive safety data. No, for the DME indication. The Agency expects the BLA to be supported by 1 year or longer efficacy data. The Agency expects a BLA to be supported by at least 2 years of safety data.

Roche August 27, 2018, response: The Sponsor acknowledges the Division's feedback. We would like to discuss the BLA submission plans as part of Question 6.

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
09/24/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119225

MEETING MINUTES

Hoffman-La Roche Inc.
Attention: Jay Bordoloi, Pharm.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Bordoloi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO6867461. We also refer to the meeting between representatives of your firm and the FDA on April 24, 2018. The purpose of the meeting was to discuss the development of RO6867461. 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 Ms. Diana Willard, Chief, Project Management Staff at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial 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:	April 24, 2018 from 12:00 PM to 1:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 119225
Product Name:	RO6867461
Indication:	diabetic macular edema
Sponsor Name:	Hoffman-La Roche Inc.
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Diana Willard

FDA ATTENDEES

Wiley Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, M.D.	Clinical Team Leader, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Martin Nevitt, M.D.	Clinical reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Abhay Joshi, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Chefo Solomon, Ph.D.	Statistical Reviewer, OB/DBIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Supervisor, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Aling Dong, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Nasim Roosta	Reviewer, Division of Medication Error Prevention an Analysis
Susan Kirshner, Ph.D.	Review Chief, Office of Product Quality (OPQ)/Office of Biotechnology Products (OBP)/ Division Biotechnology Review and Research III (DBRR III)

Steven Bowen, Ph.D.	Product Quality Team Lead, OPQ/OBP/DBRR III
Zhenzhen Liu, Ph.D.	Product Quality Reviewer, OPQ/OBP/DBRR III
Joseph Franklin, J.D., Ph.D.	Associate Director for Policy, Office of New Drugs (OND)/Therapeutic Biologics & Biosimilar Staff (TBBS)
Christopher Koepke	Regulatory Counsel, OND/TBBS
Leila Hann	Science Policy Analyst, OND/TBBS
Diana Willard	Chief, Project Management Staff, DTOP

ROCHE ATTENDEES

Karen Basu, Ph.D.	Project Lead Statistician, Biostatistics
Tim Burkoth, Ph.D.	Global Regulatory Leader, Regulatory Affairs
Nilesh Mehta	Life Cycle Leader, Global Product Strategy
Jason Ehrlich, M.D. Ph.D.	Global Head, Clinical Ophthalmology, Product Development Clinical Science
Hugh Lin, M.D.	Clinical Science Leader, Clinical Ophthalmology
Matt Meldorf, M.D.	Franchise Head, Regulatory Affairs
Aaron Osborne, M.D.	Global Development Team Leader, Clinical Ophthalmology
Jay Bordoloi, Pharm.D.	U.S. Regulatory Leader, Regulatory Affairs

BACKGROUND

A January 22, 2018, Meeting Request from Hoffman – La Roche (Roche) requested a meeting to discuss final data from the ongoing Phase 2 diabetic macular edema (DME) study BP30099, discuss a proposed Phase 3 DME protocol, and obtain feedback on issues remaining from the November 17, 2017, Type C meeting between Hoffman-La Roche Inc. and the Division of Transplant and Ophthalmology Products for this IND.

A January 26, 2018, Meeting request Granted letter listed April 24, 2018, as the agreed upon meeting date. The Meeting Package was dated and received March 1, 2018. Meeting Preliminary Comments were sent April 17, 2018, with the exception to the response to Question 8. The response to Question 8 was sent on April 20, 2018.

Roche provided feedback to the Agency's preliminary comments on April 20, 2018.

DISCUSSION

Following, in **bold font**, are the questions in the March 1, 2018, Meeting Package. The FDA responses to these questions are in *italic* font. The responses received via e-mail from Hoffman-La Roche (Roche) are in ***bold italic*** font. The April 24, 2018, meeting discussion is in regular font.

1. Pharmacology/Toxicology

Does the Agency agree that the completed nonclinical program is adequate to support the following?

- **Phase III DME studies for RO6867461**
- **Submission of a BLA for RO6867461 with no requirement for additional nonclinical studies**

FDA Response:

a. *For the Phase 3 DME clinical trials for RO6867461, we concur.*

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

b. *For the BLA, provide an adequate monkey embryofetal development (EFD) study for RO6867461. Include dose(s) that achieves clinically-relevant exposures for the period of organogenesis (e.g. gestation days 20-50 for the cynomolgus monkey).*
   i. *We recommend considering whether exposure can be maintained in pregnant monkeys for the full 30 days, or whether staggered dosing (e.g., one cohort dosed GD20-35, and another cohort dosed GD35-50 per dose level) is needed.*
   ii. *For monkeys dosed by intravenous bolus twice (D1 and D14; report # 1053363), anti-drug antibodies (ADA) were not observed at D8, and ADA responses on D15 and D17 did not affect TK. For monkeys dosed by intravenous bolus three times (D1, 29, 57; report # 1053361), the authors reported that 2/10 monkeys had reduced TK attributed to ADA detected at and after D29.*

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

c. *For the BLA, as part of your assessment of developmental toxicity, summarize the Ang2 homozygote and heterozygote knock out mice data, and provide supporting papers (e.g. Hammes et al. 2004; Dellinger et al. 2008; Gale et al. 2002;, Shimoda et al. 2007; Feng et al. 2008; Benest et al. 2013).*

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

d. *From a nonclinical perspective, we consider the data for your vanucizumab relevant to safety of RO6867461, including toxicity to female reproductive organs. For the IND, please include relevant publications in the annual reports (e.g. Kienast et al. 2013; Stubenrauch et al. 2015; Bessho et al. 2015; Kloepper et al. 2016; Hidalgo et al. 2018).*

Roche's April 20, 2018, response: The Sponsor clarifies that Development Safety Update Reports (DSURs) are provided for this IND in lieu of IND annual reports.

This feedback will be considered during the 2018 DSUR preparation. No further discussion is needed.

e. *As a regulatory issue, the determination regarding the need for carcinogenicity studies is formally made at the time of application review. In the BLA, please include a written request for waiver of carcinogenicity studies. In the BLA, please address the topic of carcinogenicity (e.g. based on mechanisms of action).*

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

2. <u>Clinical/Phase III Study Design</u>

Does the Agency agree that the proposed Phase III pivotal study design would be sufficient to support a BLA for the indication of treatment of patients with DME? In particular, does the Agency agree with the:

a) Study population?

FDA Response: We agree but you should be aware that the exclusion of subjects who are at high-risk for PDR may affect your assessment and potential labeling of the secondary DRSS endpoint.

Roche's April 20, 2018, response: The language around the PDR exclusion criteria in the protocol (Appendix 1 of pre-meeting package) provided to the Agency is incorrect. The protocol lists the following ocular exclusion criteria for the study eye:

(b) (4)

The corrected language is as follows:

"Patients who meet any of the following exclusion criteria for the study eye will be excluded from study entry:

- ***<u>High-risk PDR</u> in the study eye, as assessed by the investigator, using the following established criteria for high-risk PDR:"***

The above correction reflects the Sponsor's intention to allow enrollment of patients with PDR and to only exclude patients with high risk PDR. This revised wording will be in the final protocol. We would like to confirm this approach would not affect assessment and potential labeling.

In addition, the Sponsor is considering certain updates to the protocol prior to finalization and would like to discuss any associated considerations.

- ***>10% vs 12% HbA1C Exclusion criteria***
- ***3 month vs. 6 month anti-VEGF wash-out period***

Meeting Discussion: The Agency noted the revision that Roche states will be made in the final protocol regarding high risk PDR; the Agency also noted that the response to this question regarding labeling could still potentially apply, as the overall population enrolled in the trials will be taken into consideration when labeling is reviewed.

Regarding the additional revisions Roche proposes to the protocol, the Agency stated that the change in HbA1C exclusion criteria and a 3-month anti-VEGF wash-out period are acceptable. Roche noted that the proposed change to the wash-out period is based on what their consultants identified as more applicable to current clinical practice.

b) Treatment regimens?

FDA Response: We agree. However, the Agency believes it would be difficult to identify the population that would benefit from the proposed personalized treatment interval (PTI) dosing regimen.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback and would like to discuss this topic.

Meeting Discussion: Based on the inclusion/exclusion criteria written in the protocol, Roche stated that they believe that potentially all patients could benefit from the PTI dosing regimen. They believe both AT arms achieve similar VCA results, while there are less injections in the PTI arm. The Agency stated that the labeling for this PTI treatment regimen will be a review issue that will not be able to be resolved until the application is reviewed.

The inclusion of an active comparator control arm was encouraged by the Agency. Descriptive statistics for comparison of the two RO6867461 regimens would be acceptable.

c) Primary endpoint assessment timepoint (BCVA change from baseline averaged over Weeks 48, 52, and 56)?

FDA Response: Yes. It is acceptable for the primary endpoint to be mean average change from baseline in BCVA from Weeks 48, 52, and 56.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

d) Primary analysis plan, including the hypothesis testing sequence in the specified populations?

FDA Response: We do not agree.

Regarding your proposed primary analysis, you have not clearly specified how the following two groups of subjects will be handled:

(i) Subjects who discontinue from the study drug and do not receive prohibited therapy after discontinuation of study drug and

(ii) Subjects who receive prohibited therapy or discontinue study drug due to lack of efficacy or adverse events.

For subjects in group (i), we recommend that their efficacy data collected after study drug discontinuation be used.

*For subjects in group (ii), we recommend you consider using a trimmed mean approach (*https://www.ncbi.nlm.nih.gov/pubmed/27523396*).*

In addition, we recommend that you clearly document all potential intercurrent events (such as dropouts due to adverse event or lack of efficacy or receive prohibited medication) that may affect the efficacy outcomes (see draft ICH E9 Addendum at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf *).*

Roche's April 20, 2018, response: The Sponsor thanks the Division for the feedback and would appreciate the Division's perspective on the acceptability of the use of a mixed model for repeated measurements (MMRM) as the primary analysis method, with the following clarifying definitions

(i) For subjects who discontinue from the study drug and do not receive prohibited therapy after discontinuation of study drug, all efficacy data will be included

(ii) For subjects who receive prohibited therapy efficacy data will be censored at the timing of the use of prohibited therapy or discontinuation.

Details on how the two groups of subjects will be handled would be added to the protocol and statistical analysis plan.

Additionally, the Sponsor would like to note that the expected proportion of patients who receive prohibited therapy; or discontinue study drug due to lack of efficacy or adverse events is anticipated to be low (approximately 5%).

The Sponsor will also perform sensitivity analyses using the trimmed mean approach, details of which will be documented in the statistical analysis plan. Is this plan acceptable and are there additional recommendations?

Meeting Discussion: In principle, we find your plan acceptable if the proportion of patients who receive prohibited therapy or discontinue study drug due to lack of efficacy or adverse events is low (not more than 5%).

e) Type I error control plan for the primary endpoints?

FDA Response: Agree.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

f) Type I error control plan using a graph-based multiple testing procedure for the primary endpoints?

FDA Response: Agree.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

3. Clinical/Secondary Endpoint

(b) (4)

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4. Clinical/Safety Monitoring Plan

Does the Agency agree with the proposed key aspects of the safety monitoring plan for the Phase III DME studies?

FDA Response: We agree.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

5. Clinical/Safety Database

Does the Agency agree that the proposed number of patients and patient exposure in the safety database will support a BLA submission for RO6867461 in DME?

FDA Response: We agree.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

6. Clinical Pharmacology Studies

Does the Agency agree that no additional clinical pharmacology studies (such as studies in patients with impaired renal or hepatic functions, drug-drug interaction studies or a thorough QT [TQT] study), would be needed to support a BLA submission?

FDA Response: We agree that additional clinical pharmacology studies in patients with impaired renal or hepatic function, drug-drug interaction studies, or a thorough QT (TQT) study are not needed to support a BLA submission.

We note that you plan to evaluate the impact of patients' baseline characteristics (age, renal function, liver function) or co-medications on systemic exposure to RO6867461 using a population pharmacokinetic approach with all the data from Phase 1, 2, and 3 studies. When available, please provide the findings from these analyses to further support your proposal of not conducting any drug-drug interaction studies or any additional studies in patients with renal and hepatic impairment.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

7. Clinical Pharmacology/Pharmacokinetic, Pharmacodynamic, and Anti-drug Antibody Sampling Schedule

Does the Agency agree with the pharmacokinetic (PK), pharmacodynamic (PD), and anti-drug antibody sampling collection and analysis plan in the Phase III studies?

FDA Response: For the proposed immunogenicity assessment plan, we recommend that you collect additional blood samples during the Week 4 visit.

Roche's April 20, 2018, response: The Sponsor will plan to include the additional blood sample collection at the Week 4 visit. No further discussion is needed.

8. Aflibercept as Active Comparator

(b) (4)

(b) (4)

Meeting Discussion: Roche proposes to use a 4-letter inferiority margin. The Agency agreed assuming that Roche's studies demonstrate similar efficacy results in the control arm (aflibercept group).

The Agency reiterated that labeling claims identifying RO6867461 as being superior to aflibercept would be expected to be based on the patient population that received RO6867461 or U.S.-licensed aflibercept in the absence of adequate bridging information.

(b) (4)

9. Pediatric/Initial Pediatric Study Plan

Does the Agency agree that a waiver for pediatric studies with RO6867461 for the treatment of DME will be appropriate for the Sponsor's planned iPSP submission?

FDA Response: Waivers are not granted until NDA submission and review. You should note that you plan to request a full waiver as part of your initial pediatric study plan (iPSP).

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

10. Pediatric/Proposed Pediatric Study Request and Written Request

Has the Agency issued Written Requests for existing approved ophthalmology therapies that may be applicable to RO6867461? If so, for what indications?

FDA Response: Written requests are not available publicly until after any associated exclusivity is determined.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

11. Biologics License Application Submission Plans

Does the Agency agree full approval for RO6867461 would be appropriate to pursue via the following BLA submission options:

a) A single original BLA for the treatment of DME (1 year), followed by submission of 2 year DME data during review of the original BLA (depending on final 2-year data availability)

FDA Response: We agree.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback and thanks the Division for their flexibility. No further discussion is needed.

b) (b) (4)

c) Does the Agency agree that the proposed extension cohort in China will not adversely impact the primary analysis (1 year) to support the planned United States BLA filing?

FDA Response: We agree.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

12. FDA Target Product Profile

Does the Agency have any concerns on the achievability of the outlined labeling concepts with the proposed DME Phase III program?

FDA Response: There is not enough information available for us to comment at this time. Labeling is a review issue requiring submission and review of the entire BLA. Specific comments are deferred until we have reviewed the application. Also, see Response to Question 2b.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback. No further discussion is needed.

ADDITIONAL COMMENTS

Clinical Pharmacology

We note that within the provided findings from Study BP30099, in total eight patients (5.9%) were found to be anti-drug antibody (ADA) positive and there was no apparent impact of ADAs on the systemic pharmacokinetics (PK) of RO6867461. Please provide detailed information in this regard to include the information on the observed differences (if any) in the immunogenicity rate between the treatment arm receiving 1.5 mg RO6867461 vs. the treatment arm receiving 6 mg RO6867461.

Roche's April 20, 2018, response: The Sponsor acknowledges the Division's feedback.

A summary of immunogenicity findings will be included in the Investigator Brochure (Version 8; update in-progress), which will be part of the Phase III protocol submission. More detailed information will be included in the Clinical Study Report, or as a separate population PK/PD report. No further discussion is needed.

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/s/

WILEY A CHAMBERS
05/21/2018