CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761388Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131343

MEETING MINUTES

Hoffmann-La Roche Inc.
c/o Genentech
Attention: Robyn Harrington
Regulatory Project Management
1 DNA Way, MS 451A
South San Francisco, CA 94080

Dear Ms. Harrington:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO7112689.

We also refer to the teleconference between representatives of your firm and the FDA on April 20, 2023. The purpose of the meeting was to discuss the results of the primary analysis of phase 3 study BO42162 in conjunction with the confirmatory evidence from YO42311, BO42161, and BP39144 studies as well as to review the acceptability of clinical data to support the submission of a Biologics License Application (BLA) for the proposed indication for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH).

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

If you have any questions, contact Rolanda Bailey at (240) 402-5631 or email Rolanda.Bailey@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Carrie Diamond, MD
Clinical Team Lead
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: April 20, 2023, 3:00 – 4:00 p.m. EDT
Meeting Location: Teleconference

Application Number: IND 131343
Product Name: RO7112689

Indication: Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH)

Sponsor: Hoffmann-La Roche Inc.

Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Carrie Diamond, MD, Clinical Team Lead
Meeting Recorder: Rolanda Bailey, Regulatory Project Manager

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Tanya Wroblewski, MD, Deputy Director (Acting)
Carrie Diamond, MD, Clinical Team Lead
Sabrina McClintock, DO, Clinical Reviewer
Rosanna Setse, MD, MPH, PhD, Deputy Director for Safety

Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Lead

Office of Biostatistics (OB) Division of Biometrics IX
Yeh-Fong Chen, PhD, Supervisor
Lola Luo, PhD, Primary Reviewer

Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DMEPA)
Sue Black, PharmD, Safety Evaluator

Office of Medication Error and Prevention and Risk Management (OMEPRM), Division of Risk Management (DRM)
Jacqueline Sheppard, PharmD, Team Lead
Sarah (Katie) Holman, PharmD, Risk Management Analyst

Office of Regulatory Operations (ORO)
Julie Van der Waag, Director, Project Management Staff
Rolanda Bailey, Regulatory Project Manager

SPONSOR ATTENDEES
Anita Appius, Ph.D., Global Development Leader
Nadiesh Balachandran, Associate Safety Director
Simon Buatois, Pharm.D., Ph.D., Clinical Pharmacology Leader
Ana Maria Bühlmann, Regulatory Program Director
Sammy Chebon, Principal Statistical Scientist
Lauren Dam, MS, Regulatory Program Manager
Ruchi Gupta, MS, Regulatory Program Director
Robyn Harrington, Senior Regulatory Group Director
Gavin Ling, MBBS, FRCPath, Ph.D., Lead Clinical Director
Himika Patel, PharmD, MS, Senior Clinical Scientist
Sasha Sreckovic, M.D., Safety Strategy Leader
Sven Stanzel, Ph.D., Senior Principal Statistical Scientist
Ben Stewart, Lifecycle Leader

1.0 BACKGROUND

RO7112689, also referred to as crovalimab, is an anti-complement component 5 (C5) monoclonal antibody being developed for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH).

IND 131343 for RO7112689 was submitted on March 2, 2020. Orphan drug designation for PNH was granted on September 5, 2017.

The Sponsor plans to submit a Biologics License Application (BLA) for RO7112689 in support of the indication: “for the treatment of patients with paroxysmal nocturnal hemoglobinuria.” The application will be based on the primary analysis from the pivotal study BO42162 (COMMODORE-2), an ongoing phase 3, global, randomized study in treatment-naive patients with PNH. The submission will be further supported by data from BO42161(COMMODORE-1), YO42311 (COMMODORE-3), and BP39144 (COMPOSER) studies.

The main purpose of the pre-submission meeting is to discuss the outcome and key conclusions of the primary analysis of the pivotal phase 3 COMMODORE-2 study, along with the confirmatory evidence from the supportive studies COMMODORE-3,

COMMODORE-1, and COMPOSER, and to review the acceptability of the available clinical data to support a BLA submission in the proposed indication. In addition, the Sponsor is seeking agreement on the draft Risk Evaluation and Mitigation Strategy (REMS) proposal.

FDA sent Preliminary Comments to Hoffmann-La Roche Inc. on April 18, 2023.

2.0 DISCUSSION

2.1. Questions and Responses

Question 1: The Sponsor intends to submit a BLA supported by efficacy and safety data from pivotal study BO42162 along with confirmatory evidence from studies YO42311, BO42161, and BP39144, to enable the following indication: "Crovalimab is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria."

a) Does the Agency agree that the efficacy and safety results from the pivotal phase 3 study BO42162 along with data from the supporting studies to be included in the BLA provide sufficient and clinically meaningful evidence to characterize the benefits and risks of crovalimab in patients with PNH and support a BLA filing?

b) Does the Agency agree that the data support the above proposed indication?

FDA Response to Question 1:

a) Your pivotal study BO42162 (COMMODORE-2), is a phase 3, randomized, open-label, active-controlled, global multi-center study to evaluate the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) of RO7112689 compared to eculizumab in 210 treatment naïve patients with PNH. Patients were randomized 2:1 to receive RO7112689 or eculizumab during the primary treatment period.

Based on the results described in the meeting background package, the study demonstrated non-inferiority of RO7112689 compared with eculizumab treatment for the co-primary endpoints of hemolysis control and transfusion avoidance. Hemolysis control was defined as lactate dehydrogenase (LDH) ≤1.5x ULN from Week 5 through Week 25. The odds ratio for hemolysis control (RO7112689 versus eculizumab) was 1.02 with a lower limit of the 95% confidence interval (CI) of 0.57, which was higher than the pre-defined non-inferiority margin (NIM) of 0.2. In addition, the difference in proportion of patients with transfusion avoidance (TA) from baseline to week 25 (RO7112689 compared to eculizumab) was − 2.8% with a lower limit of the 95% CI of − 15.67%, which was higher than the predefined NIM of −20%. Secondary efficacy endpoints including breakthrough hemolysis from baseline through Week 25 and hemoglobin

stabilization from baseline through Week 25 were also reported to meet non-inferiority.

Your submission is further supported by data from the three studies described below:

- **Study BO42161 (COMMODORE-1) is a phase 3, randomized, open-label, active-controlled, multi-center study in 86 patients with a history of well controlled PNH and treated with eculizumab. Patients were randomized 1:1 to receive RO7112689 (arm A) or eculizumab (Arm B) during the primary treatment period of 24 weeks. Patients on eculizumab (Arm B) could switch to RO7112689 after the main treatment period. Efficacy results are descriptive.**

- **Study YO42311 (COMMODORE-3) is a phase 3, single-arm, multi-center study evaluating the efficacy, safety, PK, and PD of RO7112689 in 51 treatment-naïve Chinese patients with PNH.**

- **Study BP39144 (COMPOSER) is a phase 1/2 study in healthy volunteers, and 18 patients with treatment naïve PNH, and 26 patients who switched to RO7112689.**

Notable safety findings include one patient in clinical trials with a meningococcal infection. In addition, in switch patients, type III hypersensitivity adverse events (AEs) were reported, which were Grade 1-2 in severity.

The data provided in the meeting package appears sufficient to support a BLA submission; whether or not the application is fileable will be determined after the BLA is submitted. Please see statistical comments regarding COMMODORE-2 below. In addition, given very few patients from the United States were included in clinical trials please include a discussion of the applicability of foreign data to the U.S. population in the BLA submission. You should include any differences in PNH disease management and disease characteristics. (b) (4)

Statistical Comments regarding study COMMODORE-2:

- **For the primary analysis population, we recommend the intent-to-treat (ITT) population, which includes all subjects as randomized, for the primary and secondary endpoints analyses because randomization fairly distributes patients to treatment arms. As sensitivity analyses, you can use Per Protocol Population and**

your Primary Analysis Population, defined as all randomized patients receiving at least one dose of assigned treatment and having at least one centrally processed LDH level assessment after the first intravenous (IV) infusion, to assess the robustness of the study results.

- **For the primary analysis of co-primary endpoints, proportion who achieved TA and proportion of patients with hemolysis control, missing assessments should be treated as non-responses. Further, we would like to emphasize that the number of patients not being evaluated for the primary and key secondary efficacy endpoints should be kept to a minimum. Too much missing data will undermine the reliability and confidence of the results. Multiple sensitivity analyses based on different assumptions for the missing data mechanisms (i.e., MAR, MNAR) as well as different imputation techniques (e.g., MI, tipping point analysis, etc.) should be performed to examine the potential impact of the missing data on the estimation of the treatment effect. For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.**[1]

b) The indication statement will be determined during the BLA review. It is unclear if your data will be able to support a pediatric indication, given only 11 pediatric patients all of whom were ≥ 40 kg were included in your studies. This will also be determined during the BLA review.

Meeting Discussion for Question 1:

The Agency noted that the Sponsor had included the following statement in the meeting background package, "Given the need for clinical judgement of the patient's overall presentation in determination of a transfusion, investigators were ultimately entrusted to make the final decision on whether a transfusion should be administered or not." The Agency stated that the BLA submission, should address how the Sponsor mitigated bias on transfusion decisions given that the trial was open-label.

Regarding the analysis population, the Agency acknowledged that the intent-to-treat (ITT) population in a non-inferiority (NI) study may potentially bias results toward the alternative hypothesis due to study quality issues such as protocol violations and early study discontinuations; however, the Agency clarified that the ITT population should still be considered as the primary analysis population for major efficacy endpoints in NI studies because randomization fairly distributes subjects into treatment arms. Additionally, sensitivity analyses

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

based on different analysis populations such as per-protocol or any modified ITT should be performed and any disagreement between the primary analysis result and these sensitivity analyses results would raise concerns about the robustness of the estimated treatment effect. The Sponsor referred to a previous communication, dated 19 March 2020, that the Agency did not object to the Sponsor's proposed primary analysis population and suggested that ITT along with per protocol (PP) population can be used as sensitivity analyses. The Sponsor stated that the only difference between their proposed primary analysis population and the ITT population is that 1 patient in the crovalimab arm did not have a post-baseline LDH assessment, therefore, was not included in the primary analysis population. Further, the Sponsor stated that the results from the ITT analysis population agree with the primary analysis result. The Agency acknowledged Sponsor's rationale and stated that it will be a review issue.

The Sponsor clarified their primary missing data handling strategy for the co-primary endpoints, transfusion avoidance (TA) and hemolysis control, and provided their rationale for not treating missing data as non-responders. Since the study has been completed and data analyzed, the Agency stated that the Sponsor should assess these endpoints based on the methods pre-defined in the protocol/SAP for dealing with missing data. Further, the Sponsor presented results from the sensitivity analyses conducted to assess the impact of missing data on the estimation of hemolysis control. The Agency acknowledged Sponsor's reports and stated that it will be a review issue.

Question 2: Does the Agency agree with the Sponsor's draft Risk Evaluation and Mitigation Strategy (REMS) proposal?

FDA Response to Question 2:
Based on the information available at this time, a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks of meningococcal infection. Therefore, we agree that a proposed REMS should be submitted with your application. We have no specific concerns at this time regarding the REMS Document submitted with the Type B Pre-BLA meeting package, however, a complete review of the REMS, in conjunction with the full clinical review of the BLA will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

Meeting Discussion for Question 2:
The Sponsor accepted the Agency's response; no discussion occurred.

Question 3: Does the Agency expect to convene an Application Orientation meeting for this BLA application?

FDA Response to Question 3:
Yes, we will likely request an Application Orientation meeting.

Meeting Discussion for Question 3:
The Sponsor accepted the Agency's response; no discussion occurred.

3.0 ADDITIONAL IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that a draft REMS should be submitted with your application.

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

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[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*.

[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

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

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 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 PFDA is

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

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 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.

4.0 ATTACHMENTS AND HANDOUTS

See attached Sponsor's pre-meeting handout

11 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

CARRIE E DIAMOND
05/17/2023 08:20:07 PM

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B(EOP)
Meeting Category: End of Phase 2/Pre-Phase 3

Meeting Date and Time: July 17, 2019; 9:00 -10:00 AM EST
Meeting Location: White Oak Building 22, Conference Room: 1313

Application Number: PIND 131343
Product Name: crovalimab
Indication: paroxysmal nocturnal hemoglobinuria (PNH)
Sponsor Name: Hoffman-La Roche Inc. c/o Genentech, Inc.

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Rosa Lee-Alonzo, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann T. Farrell, MD, Director
Tanya Wroblewski, MD, Clinical Team Leader
Patricia Oneal, MD, Clinical Reviewer
Mitchell Anscher, MD, Clinical Reviewer
Rosa Lee-Alonzo, PharmD, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Olanrewaju Okusanya, MS, PharmD, Clinical Pharmacology Team Leader
Hisham Qosa, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Statistics Team Leader
Yaping Wang, PhD, Statistics Reviewer

Office of Pharmaceutical Quality/Office of Biotechnology Products
Brian Janelsins, PhD, Product Quality Team Leader
Shadia Zaman, PhD, Product Quality Reviewer

Center for Device and Radiological Health
Rita Lin, MS, Human Factors Consultant

SPONSOR ATTENDEES

Genentech/Hoffman-La Roche Inc.
Anita Appius, Global Development Leader
Gabriele Bieska, Global Regulatory Leader
Robyn Harrington, Associate Group Director, Regulatory
Calvin Lee, MD, Associate Medical Director
Gallia Levy, MD, PhD, Group Medical Director
Ashley Magargee, Lifecycle Leader
Ido Paz-Priel, MD, Medical Director
Alexandre Sostelly, PhD, Clinical Pharmacology Lead
Sasha Sreckovic, MD, Safety Science Leader
Marianne Uguen, Statistician
Nancy Valente, Senior Vice President, Product Development
Charlotte Vignal, Project Lead Statistician

Via teleconference
Cecile Avenal, Biologics Analytical Development
Florian Cymer, Biologics Analytical Development
Michaela Helmbrecht, Manager Technical Regulatory Affairs
Stephanie Horn, Technical Regulatory Affairs
Elisabeth Kirchisner, Technical Regulatory Affairs
Remy Kohler, Human Factors Engineer

1.0 BACKGROUND

Hoffman LaRoche/Genentech requested a Pre-Phase 3 meeting to discuss their study design of pivotal trials for paroxysmal nocturnal hemoglobinuria (PNH) and other development plans (clinical pharmacology, nonclinical, CMC) for crovalimab under PIND 131343.

Crovalimab is a recombinant humanized anit-C5 monoclonal antibody being developed for the treatment of adult and adolescent patients ≥ (b)(4) years of ages with paroxysmal nocturnal hemoglobinuria (PNH).

FDA sent Preliminary Comments to Hoffman LaRoche/Genentech on July 12, 2019.

2.0 DISCUSSION

2.1. Safety

Question 1: *Does the Agency agree with the proposed safety monitoring plan implemented in crovalimab studies? Specifically, does the Agency agree with*

Reference ID: 5402502

a) *The Sponsor's assessment that AEs occurring in patients who switched from eculizumab to crovalimab in Part 3 of the COMPOSER study are suggestive of drug-target-drug complex (DTDC) mediated reactions with clinical manifestations similar to serum sickness?*
b) *The proposed risk-management approach to minimize and mitigate these AEs?*
c) *The proposed safety database for registration of crovalimab in patients with PNH?*

FDA Response to Question 1:

a) Yes, it appears, based on information provided to date, that the AEs occurring in patients who switched from eculizumab to crovalimab are suggestive of DTDC mediated reactions with manifestations consistent with a type III hypersensitivity reaction. Although you postulate that more severe type III hypersensitivity reactions are unlikely, collection of safety data in a larger safety population will be important to assess for occurrence of more severe reactions.

b) We recommend that you submit the safety data for the 10-15 patients that will be switched from ravulizumab to crovalimab prior to embarking on phase 3 studies to ensure that the risk is not higher in these patients. Ravulizumab has a longer half-life compared to eculizumab which might increase the risk of DTDC toxicity.

We reiterate our recommendations provided to you in the Preliminary comments for the MIDD meeting:

- You will need to develop an immunogenicity assessment plan to address the risk of development of ADA against crovalimab, eculizumab, and/or DTDCs in eculizumab pre-treated PNH patients. You should assess the impact of these potential ADAs (including binding ADAs) on the clearance of crovalimab, eculizumab, and DTDCs and the safety of crovalimab.
- Given that DTDCs with eculizumab and crovalimab persist well after eculizumab is expected to be washed out of the body, it appears that the DTDCs may be acting as a reservoir for eculizumab, resulting in long-term re-exposure to eculizumab. You should address how this affects the potential risk for development of ADA to eculizumab or DTDCs.
- Switching patients between crovalimab and eculizumab may result in higher and extended risk of DTDCs formation and potential adverse events. You should propose your plan for patients that are not able to tolerate crovalimab. If they will be switched back to another complement inhibitor, details on how they will be monitored should be provided.

c) It is too premature to discuss the adequacy of the safety database to support a marketing application for crovalimab in patients with PNH.

Discussion: There was no discussion.

2.2. Clinical/Statistical

Question 2: *Does the Agency agree with the proposed clinical development program for crovalimab in PNH to support the following indication: crovalimab is indicated for treatment of adult and adolescent patients ≥(b) (4) years of age with PNH? In particular, pivotal studies for*

a) Patients who switch from eculizumab to crovalimab, including
- *the design of Switch Study BO40574*
- *the intrapatient comparison*
- *the timing of the primary analysis at 24 weeks*
- *the primary and secondary endpoints*

FDA Response to Question 2:

a) No. We do not agree with the proposed Switch Study design of BO40574. It is not an adequate and well-controlled study and it is not appropriate to use the study LIS BA41510 as the comparator arm. It is not appropriate to claim the non-inferiority maintenance effect of crovalimab vs. eculizumab. Unknown or uncontrolled bias and/or confounders may influence the study results. In addition, the current study design does not allow for comparative safety data which will be critical in the assessment of the risk profile of the drug.

In general, we recommend two well-controlled trials for an indication. Given that you are no longer pursuing the treatment-naive population, we recommend two randomized non-inferiority studies for patients who are clinically stable after having been treated with complement inhibitors (i.e., one study in patients clinically stable with treatment with eculizumab for at least 6 months and one study in patients who have received ravulizumab for at least 6 months). Patients in each study should be randomized to either continue eculizumab/ravulizumab or to switch to crovalimab. Provide the details regarding the non-inferiority margins for each of these studies.

The proposal to use hemolysis measured by LDH percent change from baseline to Day 183 or 26 weeks as the primary endpoint is reasonable; however, demonstration of a change in a meaningful clinical benefit such as transfusion avoidance will be critical. Thus, we recommend that you consider making transfusion a key secondary endpoint or a co-primary endpoint. The proposed key secondary endpoints of breakthrough hemolysis and hemoglobin stabilization appear reasonable; however, we recommend that you redesign the study for a randomized non-inferiority study as discussed above.

Discussion:
The Agency and the Sponsor had a broad discussion on the development of crovalimab in patients with PNH. The Sponsor stated (b) (4) challenges in the

Reference ID: 5402502

design and conduct of a randomized controlled trial. The Agency acknowledged the limitations and challenges that the Sponsor is encountering in conducting a randomized trial in the treatment- naïve population.

The Sponsor provided additional comments and justification as to why their proposed single-arm switch trial that relies on intra-patient comparison of patients on eculizumab who would switch to crovalimab would provide for a robust trial design.

The Agency expressed several concerns with the proposed Switch Study B040574 and the intra-patient comparison trial design to include lack of randomized safety data, concern about adequacy of pre-treatment intra-patient as a control, potential unknown or uncontrolled biases and confounders.

At this time, the Agency is unable to agree with the current proposed trial design but is open to further discussion with the Sponsor regarding the proposed Switch Study B040574.

The Agency encouraged the Sponsor to submit another meeting request to continue discussion on their overall development plan and trial design for crovalimab. We also recommend that you submit the SAS programs you used for sample size calculation for the Switch Study.

Question 3: *Does the Agency agree with the inclusion of patients* (b) (4) *-17 years old and with a body weight ≥40 kg in the planned Phase III studies?*

FDA Response to Question 3:
No, we have concerns of over-dosing adolescent patients with low body weight using the same adult fixed dose. We recommend that you consider a weight-based tiered dosing strategy for adolescent patients to avoid crovalimab over-exposure which might be associated with potential toxicity. We note that body weight is a significant covariate for the exposure and dosing of eculizumab, ravulizumab, and crovalimab. Given that adolescent patients will have higher eculizumab exposure, and the data used to support your crovalimab dose was based mainly on adult data, provide details to support your proposed crovalimab dosing in adolescent patients and address how higher doses may not be associated with higher rates or longer duration of DTDC toxicity and/or serum sickness.

Discussion: There was no discussion.

Question 4: (b) (4)

FDA Response to Question 4:

2.3. Clinical Pharmacology

Question 5: *Does the Agency agree that the clinical pharmacology plan supports*

a) the proposed dose and dosing regimen for the planned pivotal Phase III studies in patients with PNH?
b) that the following studies would not be needed to support registration of crovalimab:
– study in elderly patients?

[2] https://www.fda.gov/media/96018/download
[3] https://www.fda.gov/media/122971/download

– studies in patients with impaired renal or hepatic functions?
– drug-drug interaction studies?
– a thorough QT study?

c) (b) (4)

FDA Response to Question 5:

a) In general, your proposal of using modelling approach appears acceptable and supports the selected crovalimab phase 3 dose in eculizumab pre-treated patients. However, the proposed crovalimab dose is not acceptable for patients switching from ravulizumab because of the difference in the PK between eculizumab and ravulizumab that will affect the formation of DTDCs. We recommend you justify the crovalimab dose in ravulizumab pre-treated patients and submit all available data for review before start enrolling this patient cohort in the study.

We have concerns of potentially under-dosing crovalimab in heavier patients as well as over-dosing in lighter patients. As communicated previously during the MIDD meeting, you should provide justification that the proposed crovalimab dose and dosing regimens are appropriate in patients across a range of body weights. Also see response to Q3 regarding justification for the adolescent dose.

Discussion:
The Agency agreed with the proposed weight-based two-tier dosing approach of crovalimab in patients switching from eculizumab. The Agency did not agree that the same crovalimab dosing approach can be used for patients switching from ravulizumab.

The Agency recommended that a sentinel group of patients be considered to obtain clinical experience and inform their modeling and simulation prior to deciding on a dose and enrolling more ravulizumab pre-treated patients given that the sponsor has no clinical data to either inform their model or support their assumptions.

The Agency recommended that the Sponsor then submit the necessary data including the modeling and simulation results that support crovalimab dosing in patients switching from ravulizumab to the Agency for review before deciding on a crovalimab dosing regimen in these patients.

b) Yes, we agree that these studies will not be needed to support crovalimab registration.

Discussion: There was no discussion.

c) [redacted] (b) (4)

2.4. Chemistry, Manufacturing, and Controls

Question 6: *Does the Agency agree that the proposed cell-like potency assay, a liposome immunoassay, is appropriately addressing the mode of action of crovalimab and thus suitable to determine the potency of drug substance and drug product at release and during stability for Phase III and commercial material?*

FDA Response to Question 6:
Your proposed C5 liposome immunoassay (LIA) appears appropriate to reflect the presumed in vivo mechanism of action of crovalimab for the proposed indication; however, a final determination of the adequacy of the assay will be a review issue. As part of the potential mechanism of action, it appears that crovalimab inhibits membrane attack complex formation by two mechanisms; binding to intact C5 to prevent cleavage into subunits C5a and C5b and direct binding to the C5 cleaved sub-unit, C5b6. Limited information was provided in the meeting package to support that the assessment of binding and inhibition of cleavage of intact C5 is an appropriate surrogate assay to cover both potential mechanisms. To support licensure, information and data should be provided to support that the C5 LIA is a suitable surrogate assay to detect changes in crovalimab, under all relevant stress conditions, that can impact binding to C5b6.

As noted in the meeting package, crovalimab was engineered to bind to C5 in a pH-dependent manner and to enhance binding to FcRn for improved antibody recycling efficiency. Data from these assessments, and assessments showing lack of binding to Fcγ receptors and C1q, should be submitted to the IND. If an IND submission is not planned, these data should be submitted in the BLA to support licensure.

Discussion:
There was no discussion. The limited time remaining during the meeting did not allow for an opportunity for the Agency to provide feedback to the

[4] https://www.fda.gov/media/96018/download
[5] https://www.fda.gov/media/76403/download

Sponsor's approach to address the Agency's response to Question 6. As a result, the Agency committed to provide a post-meeting comment.

Post-Meeting Comment:
The Agency notes that the Sponsor plans to provide data from additional evaluations comparing the potency of light and temperature stressed samples by both assays to demonstrate the suitability of the C5 LIA to cover both mechanisms. The Sponsor plans to provide these data by licensure and asked whether these data will be acceptable to fulfill the Agency's request for additional information to support the use of the C5 LIA as the potency assay for routine release and stability testing of drug substance and drug product samples. The general approach appears reasonable, but a final assessment will be made at the time of BLA review. In the BLA submission, justification should be provided for the selected stressed samples and variant enriched fractions used in the comparison of the potency assays to ensure that the tested samples allow for evaluation of all degradation pathways that are relevant to the product. Sufficient data and information should be provided to show that the C5 LIA can detect product changes/degradation that can impact binding to C5b6, and that C5 LIA is at least as sensitive as the C5b6 LIA to detect changes in potency.

2.5. Nonclinical

Question 7: *Does the agency agree that the available nonclinical safety studies and results support the Phase III pivotal studies in adults and pediatric patients? Does the agency agree that once the monkey enhanced pre- and postnatal development (ePPND) data are available, no further studies are required to support marketing authorization, in particular, that there is no need for carcinogenicity and juvenile toxicity studies?*

FDA Response to Question 7:
With the addition of an ePPND study in cynomolgus monkeys, the Agency agrees the nonclinical package appears to support the clinical development plan. Juvenile animal studies and carcinogencity studies are not required. Final decisions on the adequacy of the package will be a review issue.

Discussion: There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration

Reference ID: 5402502

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*.[6] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[7]

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.[8]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[9] 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 are required in marketing application submissions for clinical

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[7] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[8] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[9] https://www.fda.gov/media/88173/download

Reference ID: 5402502

and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[10] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[11] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[12] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the

[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[12] https://www.fda.gov/media/88173/download

Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[13] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[14]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

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

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

[13] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[14] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

should be provided.

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

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[15] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[16]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[17]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[18]

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* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate

[15] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[16] https://www.fda.gov/media/109533/download
[17] http://www.fda.gov/ectd
[18] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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*.[19]

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

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

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

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's responses to the preliminary comments, corresponding reference document, and slide presentation for Question 4 discussion are appended.

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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/

TANYA M WROBLEWSKI
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