CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213535Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 128972

MEETING MINUTES

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

Dear Mr. Nguyen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for risdiplam (RO7034067).

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2019. The purpose of the meeting was to discuss the proposed content and format of your planned New Drug Application (NDA).

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

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
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-NDA

Meeting Date and Time: June 10, 2019, 2:00 – 3:00 p.m.
Meeting Location: FDA White Oak Building 22, Conference Room 1313

Application Number: IND 128972
Product Name: Risdiplam (RO7034067)

Proposed Indication: Treatment of spinal muscular atrophy (SMA)
Sponsor Name: Hoffmann-La Roche, Inc.

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Teresa Buracchio, MD, Clinical Team Leader
Christopher Breder, MD, PhD, Clinical Reviewer
Sally Jo Yasuda, Pharm D, MS, Clinical Safety Team Leader
Christopher Toscano, PhD, Nonclinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Products
Martha Heimann, PhD, Neurology CMC Lead

Office of Clinical Pharmacology
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer

Office of New Drugs, Ophthalmology
Wiley A. Chambers, MD
David Summer, MD

Rare Diseases Program
Gerald Podskalny, MD

Office of Surveillance and Epidemiology
Yasmeen Abou-Sayed, PharmD, Senior Risk Management Analyst, DRISK

SPONSOR ATTENDEES

Hoffmann-La Roche/Genentech, Inc.
Baljit Bettadapur, MSc, Associate Program Director, Pharma Technical
Niculae Constantinovici, MD, MPH, Senior Data Scientist
Carolyn Fisher, MSc, Senior Statistical Programmer Analyst
Paulo Fontoura, MD, PhD, Vice President, Global Head Clinical Development Neuroscience
Sabine Fuerst-Recktenwald, MD, Clinical Science Leader
Marianne Gerber, MD, Safety Science Leader
Kirsten Gruis, MD Global Head, Clinical Development, Neuromuscular
Anna Gruzman, PharmD, Regulatory Program Manager
Heidemarie Kletzl, PharmD, PhD, Clinical Pharmacologist
Tammy McIver, MSc, Senior Statistical Scientist
Lutz Müller, PhD, Non-Clinical and Toxicology Project Leader
Nilesh Narayan, Associate Regulatory Operations Director
Michael Ostland, PhD, Lifecycle Leader
Jean-Paul Pfefen, Global Development Leader
Matthew Schmidt, PharmD, Associate Regulatory Program Director
Megan Zoschg Canniere, PharmD, Global Franchise Head, Neurodegeneration & Rare Diseases, Regulatory Affairs

1.0 BACKGROUND

The sponsor is developing risdiplam (RO7034067), a SMN2 splicing modifier, for the treatment of spinal muscular atrophy (SMA).

The Division provided written responses to a March 2016 pre-IND meeting request and a Type C meeting was held in January 2018, to discuss the development of risdiplam. On December 19, 2018, a type C meeting was held to discuss the potential path for a New Drug Application (NDA) submission for risdiplam based on preliminary clinical data from FIREFISH (BP39056) Part 1.

The sponsor has requested this meeting to discuss and obtain the Division's agreement on the acceptability of clinical data from FIREFISH Part 1 with supportive data from SUNFISH (BP39055) Part 1 as the basis for an NDA submission. In addition, the

sponsor is seeking feedback on the content and format of the NDA in this pre-submission meeting. The sponsor is planning to submit the first portion of its NDA under rolling review on July 15, 2019, before submitting the complete application in August 2019.

FDA has granted orphan drug designation and fast track designation for risdiplam for the treatment of SMA on January 4, 2017, and April 5, 2017, respectively.

2.0 DISCUSSION

FDA sent Preliminary Comments to the sponsor on June 7, 2019. On June 10, 2019, the sponsor provided a handout with responses to the FDA preliminary comments and the questions to be discussed at the meeting. The sponsor's handout is attached to the minutes.

2.1. Clinical/Statistical

Question 1: Data Acceptability for NDA

Roche intends to submit an NDA for risdiplam on the basis of efficacy and safety data from FIREFISH Part 1 in patients with Type 1 SMA (at least 12 months of treatment) and SUNFISH Part 1 in patients with Type 2 and 3 SMA (at least 12 months of treatment with risdiplam). The NDA for risdiplam is intended to support the following indication:

Risdiplam is indicated for the treatment of spinal muscular atrophy (SMA).

Does the Agency agree with the following:

a) That the efficacy and safety results from FIREFISH Part 1 and SUNFISH Part 1 provide sufficient and clinically meaningful evidence to characterize the benefits and risks of risdiplam for the treatment of SMA and support the review of the NDA?

b) The above proposed indication statement, as supported by data from the studies included in the NDA?

FDA Response to Question 1:

We refer you to our prior comments in the Type C Meeting Minutes dated January 18, 2019. In general, the efficacy data that you have presented appears to show trends consistent with the data presented at the Type C meeting and may be adequate to support an NDA submission. However, we are still evaluating whether the sources of natural history data that you propose to provide to support the efficacy of risdiplam for SMA are appropriate. To assist us in our evaluation, please clarify the sources of

natural history data that you intend to include in your submission to characterize the benefits and risks of risdiplam for the treatment of SMA.

The final indication statement will be a matter of review.

Meeting Discussion:

The sponsor inquired whether datasets from SUNFISH Part 2 could be submitted to the NDA during the review cycle for inclusion in any potential product labeling. The Division indicated that there would not be sufficient time to review such data during the review period, and it would be best to submit the data as an efficacy supplement if an approval action were to be taken on the application. The Division reminded the sponsor that since this application would be part of the Program, all of the information necessary to support approval of the product must be part of the initial submission.

The sponsor clarified that no datasets would be available from the literature related to the thresholds chosen for the FIREFISH study. Datasets would be available for the patient-level data used for secondary endpoint comparisons for the SUNFISH study. The Division asked the sponsor to provide a reference for a threshold chosen as the primary endpoint for SUNFISH Part 1 (i.e., 3-point change in the HFSME).

Post-Meeting Notes:
In a post-meeting email on June 13, 2019, the Division conveyed that the proposed natural history sources may be acceptable to support the NDA application, (b) (4) The Division indicated that internal discussions regarding this issue were ongoing at the time, and that an update would be provided later.

After further internal discussion, the Division has determined that the application may be fileable based on the results of the primary endpoint analysis from FIREFISH Part 1, as the natural history of this endpoint is well-defined in the infantile-onset SMA population. (b) (4)

As the natural history of the proposed motor functional endpoints (e.g., CHOP-INTEND, HINE) is not as well-characterized in the infantile-onset SMA population, subject-level natural history data would be needed to serve as an external comparator for the potential inclusion of a detailed description of the motor functional endpoints from FIREFISH Part 1 in any approved label. Additionally, as survival is well-characterized in the infantile-onset SMA population, the Division is open to a description of survival

outcomes from FIREFISH Part 1 compared to the established natural history of survival in the disease.

Question 2: Content and Format of SCE/SCS and ISE/ISS

Does the Agency agree with the proposed content, structure, and format of the Summaries of Clinical Efficacy and Safety (SCE/SCS) and Integrated Summaries of Efficacy and Safety (ISE/ISS) in the planned NDA for risdiplam?

FDA Response to Question 2:

The proposal appears adequate.

We also refer you to Appendix A that provides general guidance on DNP's standard requests for safety analyses for NDA submissions. You should try to address the requests that are appropriate for your program.

Meeting Discussion:

The sponsor asked questions related to items listed in Appendix A: General Clinical Safety Requests.

- #6 under Adverse Events:

  All adverse events should be submitted. Designation as "treatment-emergent adverse events" should be determined based on timing of treatment administration which should be apparent from the datasets. The MedDRA versioning plan was adequate.

- #3 under Other Requests:

  The sponsor could send in key datasets from the ISS [e.g., ADSL, ADAE for advice on whether they were adequately formatted. An example of the sponsor's Legacy datasets should be sent in. The acceptability of the 'Legacy datasets' would depend on whether they could be adequately reviewed. All datasets should be in SAS Transport (.XPT) format.

Question 3: Alignment on Format and Structure of Data Submission

Does the Agency agree with Roche's approach for the provision of:

a) Raw and derived analysis datasets, as well as the readable code to be included for CDISC studies?

FDA Response to Question 3a:

We are not clear about what you mean by readable code for the studies you have described in legacy format. All electronic submissions should be in CDISC format and the coding in MedDRA in the version the study was finalized or the most recent version if it is not yet coded. Integrated summary datasets should be from the MedDRA version corresponding to that at the safety cut-off date.

Meeting Discussion:

See discussion under Question 2.

The Define file should be constructed such that a Medical Reviewer can understand the contents, and should not be written as a programming document. All variables should be defined in the main body of the text in a unique column.

b) Patient videos from FIREFISH Part 1?

FDA Response to Question 3b:

You should link video file(s) into the backbone and provide a PDF file of the video for archival purposes. The leaf title of the file(s) should be clear and indicative of the content and should include the word "video", so reviewers can quickly identify the file.

Video files can be placed in m5, under the Study Tagging File (stf) of the associated study and file tagged as “image”. Please make sure part of the leaf title states “video”.

Currently, the acceptable video file formats (for other sections other than m1.15) are .wmv and .mpg, which can be viewed with Windows Media Player, standard on reviewer workstations.

Also, video files should not be sent separately to individual reviewers, nor left out of the eCTD backbone. Any files submitted for review should always be linked into the backbone.

Additionally, you will need to comply with the guidelines with respect to patient/personal privacy regulations and electronic submission requirements. We refer you to the privacy regulation under 21 CFR 20.63 that states, “The names and other information which would identify patients or research subjects should be deleted from any record before it is submitted to the Food and Drug Administration. If the Food and Drug Administration subsequently needs the names of such

individuals, a separate request will be made." We ask that the names and faces to be removed/blurred from the video, if possible.

Meeting Discussion: There was no meeting discussion.

c) Ophthalmology Images?

FDA Response to Question 3c:

FDA requests that all ophthalmology scans, arranged by date (regardless of the type of scan) within subject be submitted.

Meeting Discussion: There was no meeting discussion.

d) Electrocardiogram (ECG) data?

FDA Response to Question 3d:

ECG waveforms should be submitted to the ECG warehouse (www.ecgwarehouse.com). In addition, an analysis dataset should be included in the ISS with ECGs from all subjects where this is available.

Additionally, the following items should be included in the submission to support the QT evaluation of your product:

a. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
b. Electronic data sets as SAS.xpt transport files and all the SAS codes used for the primary statistical and exposure-response analysis.
c. Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
d. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study

Meeting Discussion: There was no meeting discussion.

Question 4: Alignment on CRFs and Patient Narratives

Does the Agency agree with the proposed submission plan for Case Report Forms (CRFs) and patient narratives?

FDA Response to Question 4:

We agree with your plan.

Meeting Discussion: There was no meeting discussion.

2.2. Clinical Pharmacology

Question 5: Content and Format of SCP

Does the Agency consider the content of the Summary of Clinical Pharmacology (SCP) sufficient to support the proposed indication?

FDA Response to Question 5:

- As indicated in the Type C meeting minutes dated February 21, 2018, you should include the results of the comparative analysis of PK data from Part 1 and Part 2 of SUNFISH and FIREFISH studies. Information on bridging of clinical trial formulations to the to-be-marketed formulation should be also included in the NDA.
- A clinical drug-drug interaction (DDI) study with OCT-2 and MATE substrates may be needed.
- You may consider evaluating the effect of renal impairment using PopPK analyses.

Meeting Discussion:

- The sponsor clarified that Part 2 of both SUNFISH and FIREFISH studies used the to-be-marketed formulation. The sponsor indicated that in the initial NDA submission, the PK bridging of the Part 1 formulation to the to-be-marketed formulation will be based on the PK data available from the FIREFISH study. Data from SUNFISH Part 2 will not be included in the initial NDA submission; however, the sponsor proposed to provide a detailed PK comparison between the Part 1 and Part 2 formulations together with the submission of the top-line results of SUNFISH Part 2 in January 2020. The Agency indicated that, on face, these data appear capable of supporting the filing of the planned NDA. However,

the adequacy of the PK bridging would be a matter of review. Given that the comparison of the Part 1 versus Part 2 formulations from FIREFISH may be confounded by different age and body weight of infants over time in the respective groups, the Agency indicated that the sponsor should submit the PK data from Part 2 of the SUNFISH trial as soon as they become available to allow for timely review of the data.

- The sponsor indicated that no DDI is expected for OCT-2 based on the I/IC50 calculation with PK data obtained at the pivotal study. The Agency stated that, on face, the sponsor's rationale appears reasonable and the need for a DDI study will be a matter of review. Additionally, the sponsor asserted that MATE substrates are not typical medications used for the SMA patient population. The Agency asked the sponsor to include all the relevant information in the NDA submission to make a case for waiving the need for clinical DDI studies.

- The sponsor agreed with the Agency's comment regarding the evaluation of the impact of renal impairment based on the PK data obtained in the clinical studies in SMA patients using population PK analyses.

2.3. Nonclinical Safety

Question 6: Reversibility and Stage-Specificity of Male Germ Cell Effects

Does the Agency agree with the assessment that the effect of risdiplam on male germ cells in animals is a class effect that has been fully characterized with other SMN2 gene splicing modifying agents, and that:

a) Further studies in adult monkeys with sperm staging and confirmation of full reversibility are not warranted for risdiplam?

FDA Response to Question 6a:

The available nonclinical studies of risdiplam demonstrate clear evidence of testicular toxicity in juvenile and adult rat and in monkey. No additional nonclinical studies to assess male reproductive organ toxicity will be needed.

Meeting Discussion: There was no meeting discussion.

b) Proposed labeling text below is acceptable for inclusion in Sections 8.3 and 13.1 of the draft USPI, pending full Agency review of the data to be submitted in the NDA?

FDA Response to Question 6b:

It is premature to discuss labeling text at this time.

Meeting Discussion: There was no meeting discussion.

2.4. Regulatory

Question 7: Table of Contents of NDA MAA

Does the Agency agree that the collection and organization of supporting documentation as presented in the proposed overall Table of Contents for the NDA is acceptable?

FDA Response to Question 7:

The Table of Contents as presented in Appendix 7 appears acceptable.

You should follow the guidelines in ICH M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry (https://www.fda.gov/media/71551/download) and in the FDA guidance for industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (https://www.fda.gov/media/76141/download).

Meeting Discussion: There was no meeting discussion.

Question 8: Priority Review

In consideration of the unmet medical need for patients with SMA, Roche intends to request priority review for this application. Does the Agency agree priority review could be considered for the planned NDA?

FDA Response to Question 8:

Determination of the Review Status (Priority versus Standard Review) will be determined at the time the application is filed.

Meeting Discussion: There was no meeting discussion.

Question 9: Rare Pediatric Disease Priority Review Voucher

In accordance with Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and Section 529 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act), Roche plans to include a request for a Rare Pediatric Disease Priority Review Voucher in the NDA for risdiplam at the time of application submission. Does the Agency agree that risdiplam, if approved as a treatment of SMA for pediatric and adult patients, could qualify for this benefit, and support Roche's plan to submit a request for a Rare Pediatric Disease Review Voucher with the NDA?

FDA Response to Question 9:

Whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a matter of review. FDA would need to evaluate the application to determine whether the NDA is eligible for a priority review voucher. Please consult the draft guidance, "Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry", for instructions on how to submit a Rare Pediatric Disease Priority Review Voucher request and the eligibility criteria.
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf.

If an applicant seek approval in both adults and pediatric patients with the rare disease for the same indication, it will not affect voucher eligibility, as described in the guidance. However, we remind applicants seeking a voucher that – whether or not they seek approval for use in an adult population – we expect them to submit data adequate for labeling the drug for use by the full range of affected pediatric patients.

Prior to submitting an NDA, you may consider applying for a Rare Pediatric Disease Designation for this product. Please consult the draft guidance for additional information.

Meeting Discussion: There was no meeting discussion.

Question 10: Safety Update

Does the Agency agree with Roche's proposed timing and scope of the 90-Day Safety Update after submission of the NDA, including the plan to submit top-line results from the Drug-Drug Interaction Study (BP41361) (b) (4)

FDA Response to Question 10:

We agree with submission of a safety update for the studies in the risdiplam development program.

[redacted] you need to submit the clinical study report of these studies along with the datasets and analysis output to allow the review and verification of the results.

You may use results from study BP41361 to verify the findings of on the drug interaction potential of risdiplam with sensitive CP3A4 substrates such as midazolam from your PBPK model. The acceptability of the PBPK model and analyses will be a matter of review.

Meeting Discussion:

The sponsor acknowledged the request for a clinical study report (CSR) along with datasets and analysis outputs [redacted] from studies BP41361 [redacted] The sponsor stated that for study BP41361 (DDI), the CSR, datasets, and analysis outputs will be available for supplementary submission during the review of the NDA. The Agency clarified that the inclusion of the information from Study BP41361 in the label will depend on the timing of submission of this information and the availability of the resources to review it within the timelines of the NDA review.

Question 11: Alignment on Supplementary Data

Does the Agency agree with the proposal to submit the following supplemental information during review?

a) Top-line data from the primary analysis of SUNFISH Part 2

FDA Response to Question 11a:

Your proposal is acceptable.

Meeting Discussion:

The sponsor was encouraged to submit a brief high-level summary of the Sunfish part 2 data, when available, during the review period of its planned NDA.

b) Additional primary stability data after 12 months of storage

FDA Response to Question 11b:

As discussed during the Type C meeting held December 19, 2018, Office of New Drug Products (ONDP) recommends submission of 12 months long-term and 6-

months accelerated stability data for the drug substance and drug product primary stability batches in the original NDA. ONDP flexibility with respect to filing with less than full stability data is contingent on a clinical determination that submission of an NDA should not be delayed pending availability of the recommended stability package. Note that, if ONDP does recommend filing the application with 9 months long-term data, we do not commit to reviewing additional data received during the review cycle. Whether the proposed stability update, to be submitted end of November 2019 (approximately 100 days after initial NDA) is reviewed will be determined based on the available Agency resources at the time of receipt.

Meeting Discussion:

The Agency has not made a clinical determination regarding timing of the NDA submission versus the standard stability data recommendation. Such a determination may not be made until the filing review.

Question 12: Labeling

Roche has provided a draft of the risdiplam United States Prescribing Information (USPI), along with some questions posed within the document. Does the Agency have any comments on the draft USPI?

FDA Response to Question 12:

See response to Question 6b.

Meeting Discussion: There was no meeting discussion.

Question 13: Post-Marketing Commitments

Does the Agency agree with Roche's proposal for Post Marketing Commitments?

a) Two-year carcinogenicity study in rats

FDA Response to Question 13a:
As previously stated (Type C Meeting Minutes, February 21, 2018), the 2-year carcinogenicity study in rat may be conducted post approval.

Meeting Discussion: There was no meeting discussion.

b) [redacted] (b) (4)

FDA Response to Question 13b:

The need for post-market safety evaluations will be determined during the NDA review.

Please note that any post-market evaluations determined to be necessary to support the safety of your product would be post-marketing requirements.

Meeting Discussion: There was no meeting discussion.

Question 14: Advisory Committee Meeting

Does the Agency anticipate the need for an Advisory Committee to discuss the risk/benefit of risdiplam? If so, does the Agency have an estimate of the approximate timeframe for this meeting?

FDA Response to Question 14:

The necessity of an advisory committee will be determined during the review cycle.

Meeting Discussion: There was no meeting discussion.

Question 15: GMP

The Mutual Recognition Agreement (MRA) of 1st November 2017 between EMA and FDA to recognize inspections of manufacturing sites for human medicines conducted in their respective territories, allows for recognition of each other's inspection outcomes and hence for better use of inspection expertise and resources. Based on this MRA, does FDA plan to coordinate GMP inspectional activities with EMA, by only inspecting facilities residing in the US, and accepting results of inspections from EMA for facilities in the EU?

FDA Response to Question 15:

No. Currently, we are only reviewing and classifying inspection within the EU under MRA. According to the information you provided in Module 3, your drug substance manufacturing and testing facilities as well as one of the drug product manufacturing and primary packaging facilities are located in [redacted] (b) (4) For one of your drug product manufacturing and primary packaging facilities located in [redacted] (b) (4)

(b) (4)

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Meeting Discussion: There was no meeting discussion.

3.0 ADDITIONAL COMMENTS

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 or other risk management actions. It was concluded that the need for a REMS or other risk management strategies would be determined during the review of 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.
  - FDA has not made a clinical determination regarding timing of the NDA submission versus the normal stability data recommendation. This determination may not be made until the filing review.
  - The inclusion of the information from study BP41361 in the label will depend on the timing of submission of this information and the availability of the resources to review it within the timelines of the NDA review.

In addition, we note that a chemistry pre-submission meeting is scheduled for July 18, 2019. A summary of agreement reached at that meeting will be documented in the respective meeting minutes.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review 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.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[3]

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.”

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[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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)				

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 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*.[4]

[4] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Appendix A
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an

indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.

3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., MedWatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
   SI Units.

2. Provide the normal reference ranges for every laboratory value. Please ensure that appropriate pediatric reference values are used for pediatric patients.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges

j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Roche's handout received via email on June 10, 2019, in response to the FDA's preliminary comments of June 7, 2019.

14 Pages 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/

ERIC P BASTINGS
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