

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217389Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 133146

MEETING MINUTES

Verona Pharma PLC
8045 Arco Corporate Drive
Suite 130
Raleigh, NC 27617

Attention: Caroline Diaz, MA
Senior Vice President, Regulatory Affairs

Dear Ms. Diaz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ensifentrine (RPL554) inhalation suspension.

We also refer to the video conference between representatives of your firm and the FDA on April 24, 2023. The purpose of the meeting was to present the phase 3 clinical safety and efficacy results, and to obtain guidance from the Agency on the content and format for the future NDA for ensifentrine suspension for the maintenance treatment of patients with COPD.

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

If you have any questions, please call me at (240) 402-4483.

Sincerely,

{See appended electronic signature page}

Linda Ebonine, PA-C
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Regulatory Operations for Immunology
and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: Monday, April 24, 2023 at 2:00 PM EST
Meeting Location: via Video Conference
Application Number: IND 133146
Product Name: ensifentrine (RPL554) inhalation suspension
Indication: COPD
Sponsor Name: Verona Pharma
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Linda Ebonine, PA-C

FDA ATTENDEES

Sally Seymour, MD, Director, Division of Pulmonology, Allergy, and Critical Care (DPACC), Office of Immunology and Inflammation (OI)
Banu Karimi-Shah, MD, Deputy Director, DPACC, OI
Robert Busch, MD, MMSc, Clinical Reviewer, DPACC, OI
Craig Bertha, PhD, Chemistry Reviewer, Division of New Drug Products Branch IV (DNDBIV), Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Jessica Bonzo, PhD, Pharmacology/Toxicology Team Lead, Division of Pharmacology and Toxicology for Immunology and Inflammation (DPT-II)
Wei Sun, PhD, Pharmacology/Toxicology Reviewer, DPT-III
Yunzhao Ren, MD, PhD, Team Lead, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP)
Amer Al-Khouja, PhD, Clinical Pharmacology Reviewer, DIIP, OCP
Weiya Zhang, PhD, Supervisory Mathematical Statistician, Division of Biometrics III, Office of Biostatistics (OB)
Dong-Hyun Ahn, PhD, Biostatistics Reviewer, DBIII, OB
Linda Ebonine, PA-C, Senior Regulatory Health Project Manager, DPACC, OI

SPONSOR ATTENDEES

David Zaccardelli, PharmD, Chief Executive Officer
Kathleen Rickard, MD, Chief Medical Officer
Tara Rheault, PhD, MPH, Senior Vice President, Research and Development
Peter Spargo, PhD, Senior Vice President, Chemistry, Manufacturing and Controls
Caroline Diaz, MA, Senior Vice President, Regulatory Affairs
Prathibha Rao, PhD, Senior Director, Regulatory Affairs

(b) (4) Consultant

(b) (4) Consultant

1.0 BACKGROUND

Verona Pharma (Verona) submitted a Type B Pre-NDA meeting request on January 17, 2023. The purpose of the requested meeting was to present the phase 3 clinical safety and efficacy results, and to obtain guidance from the Agency on the content and format for the future NDA for ensifentrine suspension for the maintenance treatment of patients with COPD.

The Division granted the meeting as a video conference on January 25, 2023, and the meeting briefing package was received on March 17, 2023. The sponsor's questions from their briefing package are provided in *italics* followed by FDA responses in normal font.

FDA sent Preliminary Comments to Verona Pharma on April 19, 2023.

2.0 DISCUSSION

2.1. QUALITY / FORMULATION

Question 1:

Acknowledging that detailed assessment of the stability data will be a review issue, does the Agency agree that the stability program is sufficient to support the proposed retest period for the drug substance?

FDA Response to Question 1:

While the assessment of the stability data and the assignment of the retest period for ensifentrine drug substance is a review issue, we do agree that there is sufficient data to allow assignment of a retest period. The data from the clinical and developmental batches will be taken into consideration as supportive stability data, however we cannot agree that it will be sufficient to support a (b) (4)-month retest period until it is reviewed when the NDA is submitted.

Discussion:

No further discussion at meeting required.

Question 2:

Acknowledging that detailed assessment of the stability data will be a review issue, does the Agency agree that the stability program is sufficient to support the proposed shelf-life for the drug product?

FDA Response to Question 2:

The Agency generally evaluates stability data following the principles outlined in ICH Q1E, which recommends that the shelf-life estimation is based on the long-term data from a minimum of three batches of drug product. You propose to provide 18 months of long-term data for three full scale registration batches and provide 36 months of long-

term data for two half-scale supportive stability batches. Whether or not your stability data package will support an expiry period of (b) (4) months will likely depend on whether or not the data for the five batches of drug product are found to be poolable for the statistical analyses supporting the estimated shelf-life (refer to appendix B of ICH Q1E).

Discussion:

No further discussion at meeting required.

Question 3:

Does the Agency agree with the information Verona proposes to include in Module 3 of the NDA regarding additional clinical formulations (early inhalation solution formulation, (b) (4) ?

FDA Response to Question 3:

Yes, we agree.

Discussion:

No further discussion at meeting required.

2.2. NONCLINICAL

Question 4:

Does the Agency agree that the completed nonclinical package meets the Agency's requirements for filing and review of the NDA for ensifentrine for the maintenance treatment of COPD?

FDA Response to Question 4:

Pending review, your completed nonclinical package appears adequate for filing and review of the NDA for ensifentrine for the maintenance treatment of COPD.

Discussion:

No further discussion at meeting required.

Question 5:

Does the Agency agree with the proposed organization of nonclinical study reports and datasets in Module 4 of the NDA?

FDA Response to Question 5:

Pending review, we agree.

Discussion:

No further discussion at meeting required.

Question 6:

Does the Agency agree with the proposal for calculation of exposure margins to be presented in the nonclinical summaries and nonclinical overview in the NDA?

FDA Response to Question 6:

Pending review, we agree.

Discussion:

No further discussion at meeting required.

2.3 CLINICAL PHARMACOLOGY

Question 7:

Does the Agency agree that the completed clinical pharmacology package meets the Agency's requirements for filing and review of the NDA for ensifentrine for the maintenance treatment of COPD?

FDA Response to Question 7:

In general, your clinical pharmacology package appears reasonable. The adequacy of the data will be determined during NDA review.

Discussion:

No further discussion at meeting required.

Question 8:

Does the FDA agree with the primary and secondary analysis approach for the hepatic impairment study RPL554-PK-103, and the proposed analysis to be presented in the label?

FDA Response to Question 8:

Your proposed primary and secondary analysis approach for analysis of data from study RPL554-PK-103 appears reasonable. The adequacy of the data and the format and content of the labeling will be determined during NDA review.

Discussion:

No further discussion at meeting required.

Question 9:

Does the Agency agree with the population pharmacokinetic analysis plan, including the studies included and the covariates assessed?

FDA Response to Question 9:

Yes, we agree.

Discussion:

No further discussion at meeting required.

Question 10:

Does the Agency agree with the proposed presentation of clinical studies and analyses in NDA Module 2, Section 2.7.2 Summary of Clinical Pharmacology Studies?

FDA Response to Question 10:

In general, the proposed presentation of clinical studies and analyses in Module 2.7.2 appear reasonable. However, we note that you intend to provide (b) (4)



Discussion:

No further discussion at meeting required.

2.4 CLINICAL

Question 11:

Does the Agency agree that the completed clinical program provides the necessary safety and efficacy data to support filing and review of the NDA for ensifentrine for the maintenance treatment of COPD?

FDA Response to Question 11:

We agree that the completed clinical program supports an NDA submission. However, whether the NDA is fileable will be determined upon review of your submission. The final indication statement for product labeling will also be a review issue.

Discussion:

No further discussion at meeting required.

Question 12:

Does the Agency agree with the proposed organization of clinical study reports (CSRs) in Module 5 of the NDA?

FDA Response to Question 12:

We agree.

Discussion:

No further discussion at meeting required.

Question 13:

Verona intends to provide narratives and electronic case report forms (eCRFs) for all subjects who experienced serious adverse events (SAEs), deaths, or adverse events (AEs) leading to withdrawal from study or discontinuation of study medication in the NDA. Does the Agency agree with this approach?

FDA Response to Question 13:

We agree.

Discussion:

No further discussion at meeting required.

Question 14a:

Does the Agency have any additional comments on the clinical studies to be included in the ISS or on the revised ISS SAP?

FDA Response to Question 14a:

You plan to submit safety datasets only for clinical studies that are relevant to the evaluation of safety of ensifentrine for the maintenance treatment of COPD in the ISS. We reiterate our comments from January 6, 2023, stating that your NDA submission for this new molecular entity should include separate safety datasets for review from all clinical studies of ensifentrine, regardless of indication (e.g., COVID-19, asthma, cystic fibrosis).

Your revised ISS SAP appears generally reasonable. We note that risk differences with 95% confidence intervals will be presented for the proposed specified event categories. Clarify how these estimates will be calculated. In addition, we recommend the analyses be adjusted for study differences.

Discussion:

Verona Pharma stated they will provide a comprehensive ensifentrine clinical safety package in the NDA to support the Agency's review, including all data available to Verona for every subject that participated in all 22 completed clinical studies, which includes 2,192 subjects who received ensifentrine. This clinical safety package consists of clinical study reports (CSRs), subject data listings, and CDISC safety datasets, where available.

The Sponsor noted that

(b) (4)

Similarly, only legacy datasets are available from RPL554-010-2015 (in cystic fibrosis) and RPL554-COV-201 (in COVID-19).

(b) (4)

(b) (4). The Division agreed that the proposed safety data were reasonable for the Sponsor's initial NDA submission, and that a CDISC waiver for the studies noted above was reasonable. However, the Division stated that the Sponsor should be prepared to perform adequate and appropriate additional analyses on data from these studies in response to information requests should safety signals arise during the review.

Verona discussed their proposal for a risk-difference approach to safety analyses and asked whether FDA agreed with their approach that focused on pooled analyses for specific event categories adjusted for study differences. The Sponsor stated that it will provide 95% CIs adjusted for the study differences using a logistic regression approach (Ge, M. Drug Information Journal, Vol. 45, pp. 481–493, 2011), where data are sufficient to support the analysis. This will be included as an additional column in the tables. The originally planned, unadjusted confidence intervals based on Wilson scores will still be included for all categories. This latter method will provide a CI for adverse events where the counts are too low (in any study strata) to use the logistic model approach.

FDA responded that the Sponsor's approach was likely reasonable, but that they should update the ISS SAP accordingly for review.

Question 14b:

Does the Agency agree with the proposed approach for placement of the ISS in the NDA?

FDA Response to Question 14b:

Your approach is reasonable.

Discussion:

No further discussion at meeting required.

Question 15:

Does the Agency agree with the proposal for inclusion of safety data from ongoing clinical studies in the NDA?

FDA Response to Question 15:

We agree.

Discussion:

No further discussion at meeting required.

Question 16a:

Does the Agency have any additional comments on the revised ISE SAP?

FDA Response to Question 16a:

Due to the color differences between your drug and placebo products, previous Division communications recommend that you “provide additional efficacy subgroup data on all efficacy endpoints at Week 24 for the subgroup of subjects whose data on perceived treatment assignment is concordant with actual treatment assignment and the same data for those whose data on these variables are discordant.”

While we note your concerns regarding these data, we disagree with the elimination of this analysis from the ISE. Perform this analysis and include it in your ISE. Limitations with the analysis can also be noted.

In addition, your NDA submission should explicitly justify how your completed clinical program demonstrates substantial evidence of effectiveness (SEE). We refer you to the Draft Guidance to Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019 (available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>).

Sponsor Response:

As requested, Verona will provide efficacy analyses by subgroup of subjects whose data on perceived treatment assignment is concordant with actual treatment assignment and the same data for those whose data on these variables is discordant. Verona intends to perform this subgroup analysis on the following efficacy endpoints, using pooled data from the Phase 3 studies RPL554-CO-301 and RPL554-CO-302. *Does the Agency agree with this proposal?*

- **Average FEV₁ AUC_{0-12h} post-dose at Week 12**
- **Peak FEV₁ over 4 hours post-dose at Week 12**
- **Evaluating-Respiratory Symptoms (E-RS) Total Score at Week 24**
- **St. George’s Respiratory Questionnaire (SGRQ) total score at Week 24**
- **Morning trough FEV₁ at Week 12**
- **Average FEV₁ AUC_{0-4h} post-dose at Week 12**
- **SGRQ responders at Week 24**
- **Rescue medication use at Week 24**
- **Transitional Dyspnea Index (TDI) at Week 24**
- **Moderate/severe COPD exacerbation frequency over 24 weeks**
- **Time to first moderate/severe COPD exacerbation over 24 weeks**

Discussion:

The Division stated that the Sponsor’s plan was reasonable for their NDA submission, and that any further analyses could be handled through information requests during the review.

Question 16b:

Does the Agency agree with the proposed approach for placement of the ISE in the NDA?

FDA Response to Question 16b:

Your approach is reasonable.

Discussion:

No further discussion at meeting required.

Question 17:

Does the Agency agree with Verona's proposal for handling of data in the NDA from clinical sites at which significant concerns regarding data reliability and GCP noncompliance have been identified?

FDA Response to Question 17:

Your approach to excluding these subjects (77 subjects from site 1768 and 13 subjects from site 1721 in study RPL554-CO-301 and 18 subjects from site 1741 in study RPL554-CO-302) from presented analyses is reasonable.

To facilitate Agency review of safety and efficacy data, provide a separate, binary flag variable in relevant datasets that identifies these non-GCP excluded subjects.

Discussion:

No further discussion at meeting required. Verona stated as recommended, a binary flag variable that identifies the excluded subjects will be provided in the relevant datasets.

2.5 BIostatistics

Question 18:

Does the Agency agree with the proposed clinical and nonclinical datasets and formats to be included in the NDA?

FDA Response to Question 18:

The proposed clinical datasets in CDISC format for the phase 2b and phase 3 studies appear reasonable. The format of the nonclinical datasets is also acceptable. With respect to safety datasets, see the response to Question 14a.

Discussion:

No further discussion at meeting required.

2.6 REGULATORY

Question 19:

Does the Agency agree with the proposed table of contents and organization of the eCTD for the NDA?

FDA Response to Question 19:

We agree.

Discussion:

No further discussion at meeting required.

Question 20:

Verona proposes

(b) (4)

Does the Agency agree with this approach?

FDA Response to Question 20:

As noted in our comments dated January 6, 2023, we have concerns regarding the ability of the data from your development program to support

(b) (4)

Discussion:

No further discussion at meeting required.

Question 21:

Does the Agency agree with the studies to be included in the financial disclosure package in the NDA?

FDA Response to Question 21:

We agree.

Discussion:

No further discussion at meeting required.

Question 22:

Does the Agency agree with the proposal regarding the studies for which the information to support BIMO inspections will be provided?

FDA Response to Question 22:

We agree.

Discussion:

No further discussion at meeting required.

Question 23:

While Verona understands that the assignment of a Standard or Priority Review designation will occur after submission of the NDA, does the Agency have any preliminary feedback on the rationale for Priority Review?

FDA Response to Question 23:

We anticipate a standard review timeline for this application.

Discussion:

Verona believes the clinical data for ensifentrine demonstrate that it would provide a significant improvement in both safety and effectiveness over existing therapies for the maintenance treatment of COPD, and thus meets the statutory requirements for Priority Review designation. (b) (4)

They asked what type of additional data the review team would find compelling to support such a designation.

The Division referred the Sponsor to the Guidance to Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (available at <https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>) and stated that the criteria for priority review are intended for drugs that – if approved – would provide a significant improvement in safety or effectiveness. The Division agreed that COPD was a serious condition. However, the Division reiterated that there are significant uncertainties in the Sponsor's (b) (4)

Ultimately, the Division stated that the answer provided was a preliminary opinion, that the Sponsor could submit the data that they felt justified a Priority Review designation at the time of NDA submission, and that the Division would make a decision at that time.

Question 24:

While Verona understands that the decision to convene an Advisory Committee will be made after receipt of the NDA, does the Agency have any initial feedback on whether an Advisory Committee meeting is expected during the review of the ensifentrine NDA for the maintenance treatment of COPD?

FDA Response to Question 24:

The need for an Advisory Committee will be a review issue.

Discussion:

No further discussion at meeting required.

Question 25:

Does the Agency agree with the proposal for the 120 Day Safety Update?

FDA Response to Question 25:

We agree.

Discussion:

No further discussion at meeting required.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 25, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the

time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.¹

Discussion:

Verona proposes that REMS is not required for a complete NDA submission for their product. The Division agreed that this approach is likely appropriate based on the available data and reasonable for the initial NDA submission. The Division noted, however, that this could be readdressed should significant safety issues be addressed in the review that would warrant a REMS.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.² In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further

¹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

² 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>.

guidance on pediatric product development, please refer to FDA.gov.³

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 Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ 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

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.

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 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.

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.⁶

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.⁷

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹. 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

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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*.¹⁰

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

Slides/handouts used during the meeting are attached at the end of the meeting minutes document.

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

¹⁰ <https://www.fda.gov/media/85061/download>

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/

LINDA EBONINE
05/09/2023 04:58:37 PM



IND 133146

MEETING PRELIMINARY COMMENTS

Verona Pharma
8045 Arco Corporate Drive
Suite 130
Raleigh, NC 27617

Attention: Desiree Luthman
VP Regulatory Affairs

Dear Ms. Luthman:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RPL 554 (ensifentrine) inhalation suspension.

We also refer to your correspondence dated and received on February 24, 2020, requesting a meeting to discuss End of Phase 2 developmental questions.

The enclosed document constitutes our written responses to the questions contained in your March 23, 2020, background package.

If you have any questions, please call me at (240) 402-4483.

Sincerely,

{See appended electronic signature page}

Linda Ebonine, PA-C
Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE:

- Written Responses

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Application Number:	IND 133146
Product Name:	RPL 554 (ensifentrine) inhalation suspension
Indication:	Treatment of COPD
Sponsor Name:	Verona Pharma

1.0 BACKGROUND

Verona Pharma submitted a Type B (EOP2) meeting request dated February 24, 2020. Ensifentrine (RPL554) is a small molecule with a proposed dual mechanism of action (Inhibition of phosphodiesterases 3 and 4) for inhalation delivery. The focus of the EOP2 meeting is the development of this drug as a nebulized suspension for the maintenance treatment of COPD. The Division granted the meeting and the electronic briefing package was received on March 23, 2020.

2.0 DISCUSSION**2.1. Chemistry, Manufacturing, and Controls**

(b) (4)

2.2. Nonclinical

Question 5: Verona Pharma considers the ensifentrine to-be marketed (b) (4) have now been qualified for use in Phase 3 and the future marketed product. **Does the Agency agree?**

FDA Response:

Pending review, we agree.

Question 6: Verona Pharma believes that the data from the dog mechanistic study BT61JW completes the chronic non-clinical safety program for ensifentrine and supports chronic dosing in humans. **Does the Agency agree?**

FDA Response:

Pending review, we agree.

Question 7: Verona Pharma considers that the current nonclinical safety data package, together with data to be generated in the planned/ongoing toxicology

*studies will support submission of the NDA and commercialization of ensifentrine.
Does the Agency agree?*

FDA Response:

The nonclinical safety package and planned/ongoing toxicology studies appear adequate to support submission of an NDA. It is premature to discuss commercialization.

It is acceptable to conduct the fertility and early embryonic development study in rats and the pre- and post-natal development study in rats in parallel with phase 3 clinical trials. The Investigator's Brochure and Patient Informed Consent should report the lack of an assessment for effects on fertility and reproductive performance in female rats, adverse effects on male fertility in rats, and adverse findings in the embryofetal development study in rabbits. Both documents should be submitted with protocols for phase 3 clinical trials. Female and male subjects should use appropriate contraception during phase 3 clinical trials.

Additional nonclinical comments:

A safety assessment of extractables and leachables should be provided in the NDA for all primary container closure components of the device that are in contact with the drug product during storage as well as secondary container closure components where there is a potential for migration of leachables into the drug product (see USP 1664.1). See USP Chapters for 1663 and 1664 for the design of extractables and leachables studies, respectively.

2.3. Clinical Pharmacology

Question 8: *Verona believes that the clinical pharmacology plan for ensifentrine supports ensifentrine NDA submission and approval. **Does the Agency agree?***

FDA Response:

We agree that the clinical pharmacology plan for ensifentrine is adequate to support submission of the NDA.

You report that the potential effect of drugs that are BCRP inhibitors and concomitant medications such as LAMA or LABA on the systemic exposure of ensifentrine will be evaluated as part of the planned population PK analysis in Study CO-302. For this analysis we refer you to the following publication by Bonate et al. "Methods and strategies for assessing uncontrolled drug-drug interactions in population pharmacokinetic analyses: results from the International Society of Pharmacometrics (ISOP) Working Group (J Pharmacokinet Pharmacodyn. 2016 Apr, 43(2): 123-35.

2.4. Clinical

Question 9: *Verona Pharma proposes a single dose level of 3 mg BID as the ensifentrine dose to evaluate in two adequate and well-controlled Phase 3 studies in patients with COPD. Does the agency agree?*

FDA Response:

While selection of the single 3 mg dose may be reasonable based on the available data from study 205, your dose-ranging program using the to-be marketed formulation was limited. We recommend that you consider including an additional lower dose in your phase 3 program to provide dose response efficacy and safety data to support the dose selection.

Question 10a: *Verona Pharma considers the study design (e.g. population definition, background medication allowance, and primary and key secondary endpoints) supportive of the desired target label indication. Does the Agency agree?*

FDA Response:

We do not necessarily agree. We have the following comments regarding the proposed study design:

1. We recommend trough FEV1 as the primary endpoint. While average FEV1 AUC_{0-12h} is not unreasonable, results may be driven by a bronchodilatory response shortly after dosing. Therefore, for a maintenance bronchodilator, such as your product, trough FEV1 may be a more appropriate primary endpoint and will be factored heavily in the assessment of efficacy. If you do not include trough FEV1 as the primary endpoint, it should be included as a key secondary endpoint and included in the statistical testing hierarchy.
2. While you may include SGRQ-C as a secondary endpoint, SGRQ should also be included as a secondary endpoint and in the statistical testing hierarchy.
3. We do not agree with your proposal (b) (4)
a. Based on your product's characteristics, nebulized administration, and the single dose ranging study which was on top of tiotropium background, it appears that your product is intended to be used as an add-on bronchodilator. Your phase 3 program should be reflective of this intended use. In your phase 3 trials, your product should be studied as add-on therapy to existing maintenance bronchodilators. Enrolled patients should be allowed to continue on their maintenance LAMA or LABA.

(b) (4)

4. Given the severity of disease in this COPD patient population, your phase 3 protocol should include specific escape criteria for patients who experience clinical worsening during the trial and/or allow for up titration of maintenance medications as clinically indicated.
5. Consider stratification for current smoking status.

Question 10b:

(b) (4)

Does the Agency agree?

FDA Response:

You are developing a novel drug in a new class for inhalation via nebulization in a COPD population.

(b) (4)

See also response to question 10d.

Question 10c: *Verona Pharma considers the generation of a matching placebo to be not feasible (Section 14.1.9). However, Verona Pharma has implemented clinical procedures in order to sufficiently minimize bias in Phase 3. Furthermore, given that FEV1 is an objective, centrally read endpoint, and survey data from parallel group study RPL554-CO-205 has not indicated that patients are aware of their treatment assignment due to appearance, Verona Pharma considers that the risk of bias for both FEV1 endpoints and Patient Reported outcomes (e.g. SGRQ and E-RS) are reasonably precluded and will be acceptable outcomes in the Phase 3 program.*

Does the Agency agree?

FDA Response:

While we acknowledge your rationale, we continue to have significant concerns with your proposal to conduct clinical studies without a visually comparable placebo. Lack of a visually comparable placebo can impair interpretation of subjective measures such as COPD exacerbations and patient reported outcome measures, as well as effort dependent measures such as FEV1. We continue to recommend use of a matching placebo. However, as an alternative, you may consider using a non-visually matched placebo that is not clear (i.e., a different color). While imperfect,

such an approach may make it less likely that study personnel/participants become unblinded. Given the issues with blinding of placebo, include assessments of patient perception of their treatment assignment in the phase 3 trials. See the response to question 10d.

Question 10d: *Does the Agency agree with the approach to statistical analysis for the Phase 3 program?*

FDA Response:

We generally agree with your analysis population, COPD exacerbation, stratification and subgroups. However, we have the following comments:

Analyses: You proposed

(b) (4)

Missing Data: Your proposal to handle missing data by early withdrawn patients seems reasonable. However, it is not clear how you will handle missing data generated by subjects discontinuing treatment. Treatment discontinuation due to lack of efficacy or worsening of clinical status are considered as intercurrent events and you would need to explicitly define such events and state how it will be dealt. As such, we recommend you propose a primary estimand and an analytic method including missing data handling and lay out plans to assess the sensitivity of results to missing data assumptions. Refer to the recently finalized ICH E9 (R1) guidance on Statistical Principle for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical trials.

https://database.ich.org/sites/default/files/E9-1_Step4_Guideline_2019_1203.pdf.

From a regulatory perspective, we are interested in estimands using a treatment policy strategy to address intercurrent events. Therefore, to estimate such estimands, all subjects discontinuing treatment should be followed until study completion and all observed data should be included in the analyses.

Testing Hierarchy: Trough FEV₁ and SGRQ should be included in the testing hierarchy as it is clinically important and potentially to be included in the label.

Blinding: We do not necessarily agree that your proposed study procedures to maintain the blind at the sites are sufficient to minimize the risk of bias. Optimal

double-blind trial requires that treatments to be applied during the trial cannot be distinguished (by appearance, taste, etc.) either before or during administration, and that the blind is maintained appropriately during the whole trial. Lack of a visually matching placebo could lead to a trial in which unblinding is common with imbalanced dropouts between the two treatment arms and, therefore, unable to provide substantial evidence of effectiveness. Although we acknowledge difficulties in preparing a feasible and suitable matching placebo, you should have adequate standard operating procedures to guard against breaking of the blind and justify handling of such events in the statistical analysis plan.

Question 10e: *Does the Agency agree with Verona Pharma's planned safety assessments in the Phase 3 program and size of the safety database to support approval?*

FDA Response:

Your safety proposal appears reasonable. For adverse events, we recommend descriptive (i.e., no hypothesis testing or margin selection) but prospectively planned analysis to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, or rate ratio, along with a confidence interval for the metric used for comparison).

Question 11: *Based on the information and questions above as well as the background material provided in Section 14, does the Agency agree that the program described herein may, pending review, support the indication statement and desired language in the Target Product Profile?*

FDA Response:

A discussion of labeling is premature at this time. See our response to question 10a.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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*.¹ 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.²

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.³

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,⁴ as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical 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 page⁵ 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.

¹ 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>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁴ <https://www.fda.gov/media/88173/download>

⁵ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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.⁶ 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 Guide⁷ (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the 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.⁸ When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

⁶ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

⁷ <https://www.fda.gov/media/88173/download>

⁸ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

Additional information can be found at FDA.gov.⁹

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 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.

⁹ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

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 Resources¹⁰ and the CDER/CBER Position on Use of SI Units for Lab Tests website.¹¹

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.¹²

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.¹³

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for

¹⁰ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹¹ <https://www.fda.gov/media/109533/download>

¹² <http://www.fda.gov/ectd>

¹³ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

INDs not in eCTD format).

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*.¹⁴

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

¹⁴ <https://www.fda.gov/media/85061/download>

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

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

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/

LINDA EBONINE
05/11/2020 03:33:10 PM