CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215559Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 120181

MEETING MINUTES

Clementia Pharmaceuticals, Inc.
Attention: James Roach, MD
Senior Vice-President and Global Head, Rare Diseases Therapeutic Area
275 Grove Street, Suite 2-400
Newton, MA 02466

Dear Dr. Roach:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 28, 2020. The purpose of the meeting was to discuss the adequacy of your drug development program to support a future new drug application (NDA).

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

If you have any questions, call Meghna M. Jairath, PharmD, Senior Project Manager at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, MD
Director (acting)
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: July 28, 2020
11:00 am to 12:00 pm

Meeting Location: Teleconference

Application Number: IND 120181
Product Name: Palovarotene oral

Indication: Treatment for the prevention of heterotopic ossification (HO) in patients with Fibrodysplasia (b) (4) Ossificans Progressiva (FOP)

Sponsor Name: Clementia Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

Meeting Chair: Theresa E. Kehoe, MD
Meeting Recorder: Meghna M. Jairath

FDA ATTENDEES

Office of New Drugs (OND)/ Office of New Drugs Clinical (OND Clinical)/Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Ilan Irony, MD, Deputy Director (Acting)

OND/OCHEN/Division of General Endocrinology (DGE)
Theresa E. Kehoe, MD, Director (Acting)
Steve Voss, MD, Clinical Reviewer

OND/OCHEN/Division of Pharmacology and Toxicology (DPT-CHEN)
Gemma Kuijpers, PhD, Reviewer

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology/Office of Regulatory Operations, Endocrinology
Pam Lucarelli, Chief, Project Management Staff
Meghna M. Jairath, PharmD, Senior Regulatory Project Manager

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Cardiometabolic and Endocrine Pharmacology (DCEP)

Jayabharathi Vaidyanathan, PhD, Clinical Pharmacology Team Leader
Peng Zou, PhD, Clinical Pharmacology Reviewer

OTS/Office of Biostatistics and Epidemiology/Division of Biostatistics (II)
Feng Li, PhD, Biometric Team Leader
Kyunghee Song, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology (OSE)/ Office of Medication Error Prevention and Risk Management (OMEPRM)/ Division of Medication Error Prevention and Analysis (DMEPA)
CDR Deveonne Hamilton-Stokes, RN, BSN, MA, Safety Regulatory Project Manager

OSE/ OMEPRM/Division of Risk Management (DRM)
Cynthia LaCivita, MD

Office of Compliance/Office of Scientific Investigations/Division of Clinical Compliance Evaluation
Cynthia Kleppinger, MD, Senior Medical Officer

OND/Office of Rare Diseases/Pediatrics, Urologic and Reproductive Medicine (ORPURM)/ Division of Rare Disease and Medical Genetics
Tracy Cutler, Regulatory Scientist
Althea Cuff, Science Policy Analyst

SPONSOR ATTENDEES:
James Roach, MD Senior Vice-President and Global Head, Rare Diseases Therapeutic Area
David Rich, MPhil Vice-President, Global Development, Rare Diseases Therapeutic Area
Rose Marino, MD Senior Medical Director, Rare Diseases Therapeutic Area
Michael Harvey, PhD Vice-President, Drug Development, Rare Diseases Therapeutic Area
Andrew Strahs, PhD Vice-President, Biostatistics and Data Management, Rare Diseases Therapeutic Area
Olivia Popescu, MSc Director Global Regulatory Affairs, Rare Diseases Therapeutic Area
Marguerite Prevotat, Senior Director Global Regulatory Affairs, Rare Diseases Therapeutic Area
Michelle Motta Dardeno, Vice President and Head, Global Patient Safety, Rare Diseases Therapeutic Area
(b) (4)

1.0 BACKGROUND

Fibrodysplasia (b) (4) Ossificans Progressiva (FOP) is a rare disease of heterotopic ossification (HO). Currently there are no approved treatments. FOP is caused by a mutation in the bone morphogenetic protein (BMP) type I receptor ACVR1 (also known as ALK2) that leads to downstream activation of BMP bone-signaling pathways in the absence of BMP.

Clementia Pharmaceuticals Inc. initiated a clinical development program evaluating palovarotene, an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist, as a potential treatment for the prevention of heterotopic ossification (HO) in patients with FOP. Clementia filed an IND on April 28, 2014.

Palovarotene was licensed by Clementia from Roche Pharmaceuticals Inc. (Roche) (b) (4) . The Roche IND was cross-referenced in Clementia's IND for FOP.

Major regulatory milestones:

- Fast track designation on November 25, 2014
- Breakthrough therapy for the prevention of HO in patients with FOP on July 11, 2017
- Orphan drug designation for the treatment of FOP granted on July 21, 2014
- Rare Pediatric Disease designation February 7, 2019

History of sponsor's formal meetings with FDA:

1. Pre-investigational new drug application (PIND) meeting held on January 7, 2014, to obtain the FDA feedback on the proposed nonclinical; clinical; regulatory; and chemistry, manufacturing, and controls (CMC) approaches to the development of palovarotene for the treatment of FOP.

2. PIND Type C teleconference held on March 14, 2014, to obtain FDA feedback regarding specific safety data in Roche's IND (b) (4) and Data Monitoring Committee proposal with respect to Clementia's phase 2 study.

3. Type C meeting held on May 14, 2015, was to update FDA on the development of palovarotene for the treatment of FOP as it pertained to the pediatric population; and to obtain feedback on Clementia's proposed changes to the ongoing clinical trials and the overall development plan to support product registration.

4. Type C meeting held on March 1, 2017, was to gain agreement on the formation of new HO as a clinically meaningful outcome that would be appropriate as the primary endpoint in a phase 3 study, and the potential to utilize Clementia's natural history study (NHS) as the control group.

5. Type B End-of-Phase 2 (EOP2) meeting held on June 27, 2017, was to agree on the key design features of the phase 3 study, including enrollment criteria, dosing regimen, control group and safety monitoring.

6. Type B meeting held on May 22, 2018, was to discuss the potential of the phase 2 flare-up outcome data to support approval of palovarotene under the accelerated approval pathway.

7. Type B follow-up meeting held on October 23, 2018, was to discuss the potential of the PVO-1A-202 Part B outcomes for the episodic flare-up 20/10 mg palovarotene regimen to support an NDA for full approval of the 20/10 mg regimen for the treatment of children and adults with FOP. It was agreed that the available phase 2 data were acceptable for the filing of an NDA for the flare-up only palovarotene regimen in FOP.

8. Type B palovarotene flare-up only pre-NDA meetings:
   a. Pre-NDA nonclinical meeting held on February 5, 2019, to agree on the contents of the non-clinical package for the palovarotene NDA.
   b. Pre-NDA CMC meeting held on February 7, 2019, to agree on the contents of the CMC package for the palovarotene NDA.
   c. Pre-NDA clinical meeting held on February 14, 2019, to agree on the contents of the clinical package for the palovarotene NDA.

9. A teleconference held on December 4, 2019, during which a partial clinical hold (PCH) was issued by the FDA for children under 14 years of age participating in the palovarotene clinical trials following reports of premature epiphyseal closure. Clementia submitted a complete response to the PCH on April 16, 2020. FDA issued a correspondence on May 15, 2020, to continue the PCH. Sponsor plans to submit a formal response to PCH at a later date.

FDA had previously reached an agreement with Clementia regarding the submission of an NDA for palovarotene episodic flare-up only treatment (20/10 mg at the time of flare-up) using the phase 2 flare-up outcomes at 12-weeks. The recent data obtained following unblinding of Study PVO-1A-301 provides a source of information to allow an evaluation of the current risk/benefit in FOP patients. Clementia is now seeking FDA concurrence and guidance on an updated proposal for the NDA for palovarotene for the prevention of HO in adults and a subset of pediatric patients with FOP. This new proposal includes changes to the dosage regimen and proposed safety/efficacy data to be included in the file.

This NDA will be filed as a 505(b)(1) by Ipsen Biopharmaceuticals Inc. at the end of 2020 or beginning of 2021. FDA granted a teleconference for July 28, 2020.

FDA sent Preliminary Comments to Clementia on July 24, 2020. Clementia submitted slides on July 27, 2020 for further discussion at the meeting.

2.0 DISCUSSION

Sponsor's questions are repeated below in *italics*, followed by FDA's response in **bold**. The meeting discussion is in regular font.

Sponsor Question 1a: *Clementia/Ipsen proposes that the totality of the phase 2 and phase 3 data support an NDA submission for palovarotene for patients with FOP. The post-hoc analyses of the phase 3 study showing a clinically meaningful impact of palovarotene on HO formation using whole body computerized tomography (WBCT) data support the palovarotene "chronic/flare-up regimen" (5 mg daily with escalation to 20 mg for 4 weeks followed by 10 mg for 8 weeks [20/10 mg] with resumption of 5 mg daily upon flare-up resolution) for the prevention of HO in patients with FOP as the recommended dosage regimen. The phase 2, new HO flare-up outcomes at 12 weeks support the "flare-up only regimen" (20/10 mg at the time of flare-up) as a treatment option for subjects unable to tolerate the chronic/flare-up regimen. The efficacy and safety data supporting the adequacy for filing an NDA, the rationale for the specific dosage regimens and patient population eligible for palovarotene treatment, and the scope of the clinical data package to be included are presented in Section 6.1.*

Does the Division concur that the overall benefit-risk profile obtained with the palovarotene chronic/flare-up regimen in the phase 3 trial, and further supported by the phase 2 data, is sufficient to support filing an NDA for the proposed indication of prevention of HO in FOP?

FDA Response 1a: We agree that the data appear sufficient to support filing an NDA. There will be numerous review issues including the indication language; optimal dose and regimen (chronic/flare-up vs. flare-up only); the most appropriate lower age limit(s) to balance benefit/risk; dissimilarities between treated/untreated subjects (e.g. age and recent flare-up history) and potential selection bias due to non-randomized study design; inconsistencies in the data e.g. lack of flare-up treatment efficacy in <13 y/o subjects, and increase in HO event rates with palovarotene; and uncertainty related to high-HO-volume outliers.

Meeting Discussion: No further discussion.

Sponsor Question 1b: *Does the Division agree that the data proposed for submission adequately support both the chronic/flare-up and flare-up only dosage regimens?*

FDA Response 1b: We recommend that both 10/5 mg and 20/10 mg dosing

regimens be submitted as the flare-up only dosage regimens in the NDA. The mismatched subject age between 20/10 mg group and untreated/placebo group may have led to overestimation of the efficacy of 20/10 mg flare-up only dosing regimen. Clarify the more favorable p-value attributed to the much smaller 20/10 mg group (p. 46). We also note that the proportion of flare-ups with any new HO was lower with the 10/5 regimen (29% vs. 39%, Oct 2018 meeting package). Dose-related safety issues including growth arrest in children will be a major factor in assessment of risk vs. benefit.

Based on previous phase 2 data, the benefit of adding chronic 5 mg dosing to the flare-up dosing is unclear. Clarify the number of subjects in the phase 3 trial who did not have a flare episode and only received 5 mg daily dosing without flare dosing. We recommend subgroup analysis of new HO volume data by flare-up status (subjects with and without ≥1 flare-up episode during the phase 3 and NHS studies); and for subjects with ≥1 flare-up, summaries of new HO volume data by site (at flare-up sites and away from flare-up sites).

Clarify whether the chronic/flare-up data in Fig. 19 (mean new HO at flare-up site = 5,624 mm3 in 33 flare-ups) include the data from subject # (b) (6), who had new HO of 114,572 mm3 at week 19.

Meeting Discussion: No further discussion.

Sponsor Question 1c: *Does the Division agree with the proposed patient population for the NDA consisting of adults and children who are at least 8 years of age for females and at least 10 years of age for males?*

FDA Response 1c: The potential inclusion of skeletally immature patients in the labeled indication will be a review issue requiring detailed evaluation of risks and benefits in each age group.

Meeting Discussion: Clementia discussed slide 4 (proposed patient population). Clementia acknowledged that the final decision related to the approved patient population in the label will be made during review of the NDA but asked if FDA could provide any further guidance on their plan to submit a separate formal response to the Partial Clinical Hold (PCH). FDA stated that the Continue-PCH letter has all the details of our comments and once they submit a response for us to review, we can provide them with our comments. FDA is unable to provide any further comments at this time. FDA reiterated their concern about limb length discrepancy and understands that the outlier data on one patient in question was likely based on erroneous measurement entry, and is in the process of being reviewed by Clementia (slide 10).

Sponsor Question 2: *Clementia/Ipsen's analysis of the data in Study PVO-1A-301 includes the results of the Bayesian compound Poisson primary efficacy analysis, the*

Bayesian compound Poisson analysis without the square-root transformation, and the frequentist weighted linear mixed effects model (wLME).

Does the Division agree that these methods (as described in Section 6.2) are appropriate to describe the annualized new HO volume endpoint and sufficient to characterize the benefit of palovarotene in the NDA?

FDA Response to Question 2: Your proposed analyses using both Bayesian compound Poisson model and weighted linear mixed effects model will be reviewed once submitted. However, as you noted, because the futility boundary was crossed at the second interim analysis and the study data and results were unblinded, all subsequent post-hoc analyses will only have limited statistical interpretation. Furthermore, comparability of the subjects treated in Study PVO-1A-301 with those from the NHS remains uncertain and will be a major review issue.

We have the following additional comments regarding the efficacy analyses.

1. **The Poisson distribution has very restrictive assumptions that tend to result in an underestimate of the variance. Provide model diagnostics to show that your assumptions of the data distribution are appropriate in your NDA submission.**

2. **Provide a detailed evaluation of the operational characteristics of the proposed Bayesian analysis including its chance of producing erroneous conclusions and the reliability of treatment effect estimates. Submit a comprehensive simulation report along with the software codes used for simulation.**

3. **For your primary analysis, missing data are assumed missing at random. You should assess the robustness of the study results to deviation from the underlying assumptions of the primary analysis through sensitivity analyses. You state that Statistical Analysis Plan v1.2 (in preparation) will include a full list of sensitivity analyses. You should submit Statistical Analysis Plan v1.2 before submitting NDA.**

4. **You proposed a weighted linear mixed effects model as additional analyses. However, it is not clear how to implement the weighted approach with missing data. Please provide more details about the weighted approach and justifications for weighting given that the response variable is annualized new HO volume.**

5. **You have also proposed imputing data using a single imputation in multiple places throughout the submission. In general, it is not acceptable**

unless you provide a proper scientific justification. You should consider multiple imputation to impute data.

6. **In Section 4.2 of the meeting package (page 20), for PVO-1A-301, you state that the results utilizing data collected up to Month 24 are compared with those from the NHS collected up to Month 36. You should clarify why it is "up to Month 36" instead of "up to Month 24" from NHS.**

7. **In 6.1.2.1, you state that negative new HO volume is set to zero for the primary analysis based on Bayesian compound Poisson model. Please clarify how many negative new HO volume cases are observed throughout the study.**

8. **In PVO-1A-301 Analysis Report (dated May 14, 2020), Section 3.1 states that Principal Full Analysis Set (PFAS) population includes subjects who meet the ≥ 50% of regions evaluable (5 out of 9) criteria. Please elaborate this evaluable criteria. In addition, you should clarify whether this type of exclusion will be implemented in the final analysis and assess the impact of exclusion through sensitivity analysis. It also states that missing timepoints (as stated in Section 2.4.4.1 of the SAP) will not be imputed and body regions with non-evaluable HO volume at a timepoint will be represented as having no new HO and the volumes will be set to zero in the analysis. Please note that you should conduct sensitivity analyses for all missing data to assess the robustness of the study results.**

9. **You should include well-documented software programs used to generate all the efficacy datasets, tables and figures in your NDA submission.**

Meeting Discussion: No further discussion.

Sponsor Question 3: *Clementia/Ipsen's plan for submission of the clinical datasets in support of the registration of palovarotene as a treatment for FOP is described in Section 6.3.*

Is this plan acceptable to the Division?

FDA Response to Question 3: Your plan to submit completed study reports (excluding data sets) of clinical pharmacology studies completed by Roche (Studies RB16327, NP17056, NP17726, RB16328, NP17040, NP17041B, and NP21025) is acceptable. You stated that plasma drug concentration data and pharmacokinetic (PK) parameter data for studies completed by Roche are not available. The meeting package shows that you will submit a population PK

report. Clarify whether the PK data from these studies will be incorporated into your population PK analysis.

Your plan for submission of the phase 2 and 3 FOP study and NHS datasets is acceptable. Complete or interim study reports should also be submitted.

Meeting Discussion: Clementia discussed slide 5 in regards with population PK analysis and confirmed that all but 3 healthy volunteer studies (NP17056, NP17040 and NP17041B) conducted by Roche will be included in the population PK analysis. FDA stated their approach is acceptable.

Clementia further discussed slide 6 in regards with clinical study reports and stated that the CSR for all the healthy volunteer and COPD studies will be included in the NDA. FDA asked if the CSR for study PVO-1A-103 (TQT) will be submitted, to which Clementia confirmed yes. FDA further asked about how many subjects were in study PVO-1A-203. Clementia stated that 6 subjects were enrolled but not all them received the drug and the study was terminated. FDA asked if they plan to submit the complete data set for study PVO-1A-203, Clementia confirmed yes. FDA had no further questions.

Sponsor Question 4: *Clementia/Ipsen's plan for integration and pooling to be included to support the data presented in the integrated safety analysis and integrated efficacy analysis is described in Section6.4.*

Is this plan acceptable to the Division?

FDA Response to Question 4: We would reiterate our comments at the February 2019 pre-NDA meeting about inclusion in the ISS of discussion of various safety issues. The plan to not integrate phase 2 and 3 efficacy data is acceptable. Clarify your plans for presentation of ISE efficacy data by different age groups.

Meeting Discussion: Clementia discussed slide 7 about ISE and asked if this plan for the presentation of the ISE data by age groups is acceptable. FDA agreed with the proposed age groups listed on the slide and stated that they would also like to see efficacy data for both male and female subjects ≥ 12 years old.

Clementia further asked if it was acceptable that the narrative portion of the ISE be included only in Module 2.7.3. FDA stated that we would provide a post meeting comment in regards with this.

Post meeting comment: This is acceptable.

Clementia discussed slide 8 about the ISS and asked if their plan for the subgroup presentation of the ISS data by age group is acceptable**.** FDA stated that the proposal is

acceptable but that they would also like to see bone safety and other safety data on pediatric subjects ≥ 12 years old. Clementia further inquired would whether that would be for the subgroup up to 18 years of age. FDA confirmed that they would like to see the safety tables for ages ≥ 12 to 18 years old. Clementia asked FDA to clarify whether the age through 18 years includes 18 year olds. FDA stated that they would provide a post meeting note to confirm if the age 18 years old should be included or not.

Post meeting comment: After further internal discussion, there is no scientific reason to expand the regulatory definition of the pediatric population. Therefore, the upper age limit should be < 17 years.

Sponsor Question 5: *The contents of the NDA for the flare-up only palovarotene dosing regimen was formerly agreed upon with the FDA in nonclinical, CMC, and clinical pre-NDA meetings held on February 5, February 7, and February 14, 2019, respectively. For the clinical package, all components previously agreed upon during past discussions, including the food effect/drug-drug interaction study (PVO-1A-102), the TQT study (PVO-1A-103), the data collected in the seminal fluid study previously planned for post-approval (PVO-1A-104), and the data collected in the phase 2 (PVO-1A-202/204) and phase 3 study (PVO-1A-301), as well as safety data from the MO study (PVO-2A-201) will be included. The data for the ongoing studies (described in detail in Section 6.5) will be provided utilizing the data cutoff of February 28, 2020. Does the Division agree with the proposed data clinical package for the NDA as described in Section 6.5?*

FDA Response to Question 5: The proposed clinical package appears acceptable for NDA filing. We expect that your reference to "data" from each study will include complete or interim study reports in addition to datasets.

Meeting Discussion: No further discussion.

Sponsor Question 6: *Palovarotene is a member of the retinoid class of compounds. Clementia has carefully reviewed the class level Risk Evaluation and Mitigation Strategies (REMS) for marketed systemic retinoids, and other known teratogenic non-retinoid products (eg, the isotretinoin "iPledge" program, Soriatane's "P.A.R.T" program). Given the extremely small population of patients with FOP, the seriousness of the disease, the assumed benefit-risk profile of palovarotene for FOP patients, and the identified risks (including teratogenicity and PPC), there will be safety measures required to ensure that serious risks are understood by both prescribers and patients. Does the agency agree that the identified risks and safety measures as described in Section 6.6 are appropriate to serve as the basis of the safety education and training program?*

FDA Response to Question 6: At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is

necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: Clementia discussed slide 9 and stated that with respect to a REMS, they will submit a risk management strategy but do not plan to identify this as a REMS. FDA stated Clementia's plan is reasonable for filing and that they should clearly articulate the rationale in their NDA submission.

Additional Clinical Comments: Although the data in Appendix 6 show that leg length disparities did not develop in most pediatric subjects, there appears to be an extreme outlier with change in R vs. L difference of 8.65 cm during the study.

Meeting Discussion: Please see meeting discussion under Question 1c.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. Please refer to meeting discussion under Question 6.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding,

along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[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

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

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.

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.

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.[3]

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.[4]

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

[3] http://www.fda.gov/ectd
[4] 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 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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*.[7]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	August 28, 2020

6.0 ATTACHMENTS AND HANDOUTS

11 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[7] 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/

THERESA E KEHOE
08/27/2020 04:03:01 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120181

MEETING MINUTES

Clementia Pharmaceuticals, Inc.
Attention: Jeff Packman
275 Grove Street, Suite 2-400
Newton, MA 02466

Dear Mr. Packman:

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

We also refer to the meeting between representatives of your firm and the FDA on February 14, 2019. The purpose of the meeting was to discuss the New Drug Application (NDA) preparation for palovarotene.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 14, 2019, 1:00 P.M. to 2:30 P.M.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 120181
Product Name: palovarotene

Indication: Prevention of heterotopic ossification in patients with Fibrodysplasia Ossificans Progressiva (FOP)

Sponsor/Applicant Name: Clementia Pharmaceuticals, Inc.

Meeting Chair: Theresa Kehoe, M.D.
Meeting Recorder: Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive and Urologic Products (DBRUP):
Audrey Gassman, M.D., Deputy Director
Theresa Kehoe, M.D., Medical Team Leader
Stephen Voss, M.D., Clinical Reviewer
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Peng Zou, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III

OTS, Office of Biostatistics, Division of Biometrics III:
Renee Rees, Ph.D., Acting Team Leader
Mahboob Sobhan, Ph.D., Associate Director

Office of Pharmaceutical Quality, Office of New Drug Products:
Mark Seggel, Ph.D., Quality Assessment Lead

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Oyinlola Fashina, Pharm.D., Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
Laura Zendel, Pharm.D., Team Leader, Division of Risk Management (DRISK)
Courtney Cunningham, Pharm.D., Reviewer, DRISK
Jamie Wilkins Parker, Pharm.D, Deputy Director, DRISK

OSE, Office of Pharmacovigilance and Epidemiology:
Karen Konkel, Ph.D., Division of Pharmacovigilance (DPV)

Office of New Drugs, Immediate Office, Rare Diseases Program:
Melanie Blank, M.D., Reviewer

Office of New Drugs, Office of Drug Evaluation IV, Division of Pediatric and Maternal Health:
Tamara Johnson, M.D., Medical Team Leader
Denise Pica-Branco, Ph.D., Regulatory Project Manager

Division of Cardiovascular and Renal Products:
Lars Johannesen, Ph.D., Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Kuang-Heng Hsiao

SPONSOR ATTENDEES
Clarissa Desjardins, Ph.D., Chief Executive Officer
Donna Grogan, M.D., Chief Medical Officer
Jeff Packman, MBA, Chief Development Officer
Michael Harvey, Ph.D., Executive Director, Drug Development
Olivia Popescu, M.Sc., Senior Manager, Regulatory Affairs
Andrew Strahs, Ph.D., Vice President, Biostatistics and Statistical Programming
Michelle Dardeno, R.Ph., B.S., Vice President, Head Pharmacovigilance and Drug Safety
Rose Marino, M.D., Medical Director
Isabelle Lemire, Ph.D., Director, Nonclinical Research
(b) (4), Pharmcokinetics Consultant (via teleconference)

1.0 BACKGROUND

Fibrodysplasia Ossificans Progressiva (FOP) is a rare, chronic, painful, disabling, and fatal disease of abnormal bone formation. It is caused by a mutation in the bone morphogenetic protein (BMP) type I receptor ACVR1 (also known as ALK2) that leads to downstream activation of BMP bone-signaling pathways in the absence of BMP. Clementia is developing palovarotene for oral administration to treat FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist.

Orphan drug designation for treatment of FOP was granted on July 21, 2014. Fast Track designation for prevention of heterotopic ossification following preosseous flare-ups in patients with FOP was granted on November 25, 2014. Breakthrough therapy designation was granted on July 11, 2017, for the prevention of heterotopic ossification (HO) in patients with FOP.

The FDA previously met with Clementia on October 23, 2018, to discuss the available data sufficient to support submission of a New Drug Application. At that meeting, FDA agreed that the available data would support filing of a marketing application for palovarotene in prevention of heterotopic ossification associated with flare up symptoms in patients with fibrodysplasia ossificans progressive (FOP). Clementia is now requesting a meeting to discuss the NDA preparation for palovarotene.

FDA sent Preliminary Comments to Clementia on February 11, 2019.

2. DISCUSSION

General Comment:
We note that you propose a different indication in your meeting package (treatment of fibrodysplasia ossificans progressiva) than the indication which received breakthrough therapy designation (prevention of heterotopic ossification (HO) in patients with fibrodysplasia ossificans progressiva). We recommend that you keep the indication language consistent with the breakthrough therapy designation as this is the indication for which we have been providing advice.

Discussion at the Meeting:
Clementia acknowledged and agreed with the FDA's comment. The FDA stated flare related language may be added during review of the application.

Question 1: ***Clementia believes that the nonclinical pharmacokinetics package along with the planned studies described below will adequately support the registration of palovarotene in FOP (see background information and Questions 2-4 for more details). Does the Division agree?***

FDA Response to Question 1:
No, we do not agree. See our comments under Questions 2-4.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 2: ***Clementia believes that the in vivo and in vitro palovarotene biotransformation experiments conducted to date have demonstrated that the metabolic profile is well characterized, and no additional biotransformation experiments are needed. Does the Division agree?***

FDA Response to Question 2:
No, we do not agree. Assess whether CYP2B6 is responsible for the metabolism of palovarotene.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 3: ***Clementia believes that* in vitro *palovarotene CYP inhibition experiments conducted to date have demonstrated that the inhibition potential is well characterized and no additional CYP inhibition* in vitro *experiments are needed. Does the Division agree?***

FDA Response to Question 3:
No, we do not agree. Assess in vitro inhibition of palovarotene on CYP2B6.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 4: ***Given that the elimination of palovarotene is almost exclusively through biotransformation with a minimal amount of parent drug and metabolites excreted in urine, Clementia is not planning to assess palovarotene as a substrate for renal transporters OAT1, OAT3, OCT2, MATE1 and MATE2-K. This is in accordance with the FDA* Guidance for Industry *"In vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies"* issued in October 2017. *Does the Division agree?***

FDA Response to Question 4:
Yes, we agree that assessment of palovarotene as a substrate for renal transporters OAT1, OAT3, OCT2, MATE1 and MATE2-K does not appear to be warranted. However, we reiterate that you should assess whether palovarotene is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATEs (MATE-1, MATE-2K), OAT1, and OAT3.

Discussion at the Meeting:
Clementia confirmed that the NDA will include the recommended inhibition assessment. Clementia referenced the additional information submitted on January 30, 2019, to the IND regarding the Breast Cancer Resistance Protein (BCRP) transporter. The FDA acknowledged

the additional information and stated that a full study report would be needed for review of the risk assessment for this transporter. The FDA communicated preliminary concerns regarding the palovarotene solubility results provided: the solubility of palovarotene at various pH was measured in aqueous buffer at 25°C. Palovarotene is orally administered with a meal. Its solubility should be measured in biorelevant media such as fed-state simulated intestinal fluid and at 37°C. The FDA was agreeable to Clementia submitting the study report with a formal waiver request prior to submission of the NDA depending on timing of the request if the sponsor still believes a waiver is warranted after addressing the FDA's preliminary concerns.

Question 5: ***Special population PK studies to evaluate the pharmacokinetics of palovarotene in subjects with hepatic or renal impairment have not been performed. Given the reasons provided below, Clementia does not intend to perform these special population PK studies. Does the Division agree?***

FDA Response to Question 5:
Yes, your proposal appears reasonable. The lack of information in patients with hepatic impairment and renal impairment will be considered during NDA review and will likely be included in the product's labeling.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 6: ***Following the review of the information included in the "ICH E14 Guidance: the clinical evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs" and the nonclinical and clinical information included below, Clementia believes that a separate thorough QT study is not necessary for registration of palovarotene. Does the Division agree?***

FDA Response to Question 6:
No, we do not agree. Conduct a thorough QT study per the ICH E14 guideline. If you intend to use the ECG data collected in your SAD/MAD studies (RB16327/ RB16328) as a substitute for a TQT study as per ICH E14 Q&A 5.1, you must demonstrate that each trial collected robust, high-quality ECG recording and the analysis was sufficient to support a valid assay for ECG intervals. If you intend to pool data from multiple studies, you must test for heterogeneity. You must demonstrate that the doses evaluated in your SAD/MAD studies (RB16327/RB16328), will characterize the QTc at sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic dose) to waive the need for a separate positive control.

We recommend that you re-submit your justification for using these data as a substitute for a TQT study and include a statistical/modeling analysis plan. If these data cannot be used as a TQT study substitute, submit a TQT study protocol for review.

Discussion at the Meeting:
Clementia presented several slides (8-10) to explain their approach to address the potential impact of palovarotene on cardiac repolarization. Clementia characterized the Phase 1 studies (Slides 11-13) and summarized the ongoing Phase 1 study (Slide 14). Clementia proposed to submit the rationale and summarize all the data in the NDA as a substitute for the TQT study, and if the data was deemed insufficient during the NDA review Clementia would perform a TQT study as a post-approval commitment.

The FDA stated that, based on the data provided, it appears that Clementia does not have adequate data to support exclusion of small effects (10 ms). The FDA referenced the ICH E14 guideline Q&A (R3) 5.1 and explained that Clementia has not demonstrated that the included doses will characterize the QTc at sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic dose) to waive the need for a separate positive control. The FDA did not agree that any of the rationale submitted would negate the need for a TQT study. Clementia clarified that conducting a TQT study would not be feasible based on timing for a planned September 2019 NDA submission. The FDA agreed to further discuss the issue internally and provide additional feedback in a post-meeting comment.

The FDA suggested that Clementia consider the feedback from all three recent sponsor meetings in the context of timing of the NDA submission and optimizing the likelihood for a first-cycle approval.

Post-Meeting Comment:
FDA continues to recommend Clementia conduct a TQT study, in light of the contradictory nonclinical data.

Question 7: ***Based on the rationale provided below, does the Division agree that the data included in the NDA are sufficient to support label dosing instructions in which palovarotene capsules may be swallowed whole or sprinkled on soft foods?***

FDA Response to Question 7:
No, we do not agree. In your relative bioavailability study for sprinkles, add two additional treatment arms for capsule contents sprinkled on yogurt (b) (4) if you plan to list yogurt (b) (4) in your product labeling. In addition, we reiterate that the to-be-marketed formulation of palovarotene should be used in your proposed food effect study.

Discussion at the Meeting:
Clementia presented (Slide 16) their rationale for the selection of applesauce and their proposal for the prescribing information: "palovarotene capsules may be swallowed whole or sprinkled on soft foods." The FDA stated that the approach was reasonable provided Clementia shows that the drug is stable in (b) (4) yogurt, and that applesauce does not have an effect on the bioavailability of palovarotene compared to the intact capsules. The prescribing information will be a review issue.

Question 8: ***Clementia's plan for submission of the clinical datasets in support of the registration of palovarotene as a treatment in FOP is described below. Is this plan acceptable to the Division?***

FDA Response to Question 8:
Yes, in general the plan is acceptable. However, clarify whether subject ID in the pooled FOP ADaM dataset will remain the same as in the original study.

Submit study reports, plasma concentration datasets (xpt format) and pharmacokinetic parameter datasets (xpt format) for the seven clinical studies listed in your meeting package, Appendix 2 (Page 41-47): single ascending dose study (RB16327), mass balance study (NP17056), age and gender effect study (NP17726), multiple ascending dose study (RB16328), rifampicin interaction study (NP17040), ketoconazole interaction study (NP17041B), and prednisone interaction study (NP21025).

Discussion at the Meeting:
Clementia clarified that any subject who appears in multiple FOP studies will be assigned a single subject ID ('USUBJID') that is used in all study-level SDTM and in the pooled FOP ADaM datasets.

Clementia acknowledged the comments regarding the PK datasets.

Question 9: ***Clementia's plan for integration and pooling to be included to support the data presented in the integrated safety analysis and integrated efficacy analysis is described below. Is this plan acceptable to the Division?***

FDA Response to Question 9:
This plan is acceptable. In the integrated summary of effectiveness (ISE), presentation of the efficacy data should include subgroups of skeletally immature and mature patients. The integrated summary of safety (ISS) should include a comprehensive discussion of bone safety in children, especially growth and epiphyseal growth plate data. In light of recent reports of tonic clonic seizure in two phase 2 FOP patients who had no prior history, include a comprehensive discussion of clinical and nonclinical evidence relevant to the risk of seizure and other neurologic, neuromuscular, and psychiatric adverse effects with palovarotene and related retinoids. The ISS should also provide analyses and discussion about other retinoid safety issues or adverse events of interest (including, but not limited to, psychiatric disorders, hepatotoxicity, pancreatitis, lipid abnormalities, hyperostosis, etc) that are included in the approved labeling of other retinoid products.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 10: ***In the FDA response to Question 1a #9 at the 23 October 2018 Type B meeting, Clementia was requested to provide code for the statistical analyses in the submission. Additional information on the inferential analyses planned for the NDA is included below. Are the methods utilized acceptable to the Division?***

FDA Response to Question 10:
The analysis methods are acceptable. However, you indicated that missing flare-up data will not be imputed and will not be included in the analysis. We expect that the dataset have an indicator variable for flares without evaluable 12-week volume of new HO volume and need to justify why missing flare-up data will not be handled.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 11: ***The 12-week flare-up HO outcome data obtained in the Natural History Study (NHS) and the Phase 2 studies as assessed by flare-up site CT scan will form the basis for the assessment of efficacy of the 20/10 mg episodic dosing regimen of palovarotene in FOP. Does the Division agree with the scope of the efficacy data to be included in the registration package to support episodic dosing of palovarotene in FOP?***

FDA Response to Question 11:
No. In addition to the 12-week flare-up data outlined, all HO data should be submitted, whether included in analyses or not. This should include jaw and upper back flare-up HO data from the NHS or phase 2 studies. In addition, submit all available whole body CT (WBCT) data, in part to help assess whether HO may continue to form at flare-up sites beyond week 12, based on two patients in studies 201 and 202:

- According to the briefing package (pp. 48-49), patient (b) (6) received treatment (10/5 mg) for two right hip flare-ups. During the first, HO at the flare-up site increased from 0 at baseline to 1102.5 mm^3 at week 12. At onset of the second flare-up at the site 4 months later, baseline HO had increased to 21912.0 mm^3.
- The briefing package for the Oct. 2018 meeting (p. 28) indicates that patient # (b) (6) received the chronic/flare-up regimen and had evaluable HO volume data only at week 19 (new HO volume of 114, 572 mm^3) and not at week 12.

Therefore, we request an analysis of the relationship between HO at week 12 and in any available scans at the same site in that patient, obtained either in a subsequent flare-up (e.g. patient # (b) (6)) or derived from the month 12 WBCT (similar to the data presented in Appendix 3 of the Oct. 2018 meeting package). This information should be summarized in palovarotene-treated and untreated (NHS or placebo) patients, and also included in the individual "subject summaries".

Discussion at the Meeting:
Clementia clarified which HO data will be included in the NDA (Slide 18). The FDA asked Clementia to address any missing data, including the reason(s).

Question 12: ***Module 5 of the NDA will be comprised of clinical study reports for Studies PVO-1A-101, PVO-1A-102, PVO-1A-201, PVO-1A-202/204 (interim), and PVO-1A-203 (abbreviated); as well as the population PK, PK/PD analysis report, integrated summaries of safety/efficacy (see Question 9), and four legacy Roche reports. The NHS protocol and associated amendments will also be included in Module 5; and NHS tabular summaries and line listings will be included in the integrated summaries of safety and efficacy. As the NHS is ongoing and continues to follow subjects annually (although flare-up imaging is no longer being performed) a clinical study report will not be included in the NDA for this study. Similarly, interim study reports for ongoing Studies PVO-1A-301 and PVO-2A-201 will not be generated, although data from these studies will be included as per Question 9. Does the Agency agree with this approach?***

FDA Response to Question 12:
No. In addition to the tabular summaries and line listings in the ISE and ISS, the NDA should include interim study reports from the ongoing studies NHS, PVO-1A-301 and PVO-2A-201. Your proposed date of March 31, 2019, is acceptable as the cut off for the interim study reports.

Discussion at the Meeting:
Clementia asked the FDA to clarify the need for interim study reports. The FDA explained that Section 505(b)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act states that full reports of the investigations to demonstrate a product's safety and effectiveness be submitted in an NDA, and not including these in the NDA submission is a possible Refuse to File issue. Clementia agreed to include the requested interim study reports.

Question 13: ***At the 23 October 2018 Type B meeting, the Division requested that Clementia provide a by-patient summary of the benefit and safety issues in addition to the flare-up analyses presented in the Type B meeting briefing document. Clementia has prepared a draft of a "subject summary" for the Division's review. Such a summary will be prepared for each FOP subject who participated in the Phase 2 studies and/or the NHS and included in the NDA.***

Does the Division agree that the "subject summaries" adequately capture the benefit and safety issues by subject?

FDA Response to Question 13:
The format and content are acceptable, with the addition of WBCT HO data relevant to the flare-up site(s) as indicated in the response to question #11.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 14: ***Palovarotene is a member of the retinoid class of compounds. Clementia has carefully reviewed the class level REMS (isotretinoin "iPledge" program, Soriatane's "P.A.R.T" program, other marketed systemic retinoids as well as other known teratogenic non-***

retinoid products). Given the extremely small patient population with FOP, the seriousness of the disease, and the assumed benefit risk profile of palovarotene for FOP patients, Clementia intends to implement a specially designed education program to ensure understanding of fetal toxicity risk by prescribers, pharmacists, and FOP patients in addition to the appropriate product labeling. Does the agency agree with the key elements of Clementia's palovarotene "educational program" that is defined below?

FDA Response to Question 14:
At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Aside from the discussion of whether a REMS is necessary, if you choose to proceed with developing educational materials, we have the following comments regarding the content of your program to address the risk of embryofetal toxicity.

Contraception:

- Define "highly effective method" in your program. Highly effective method is defined in the literature as a "typical use" pregnancy rate of less than 1% (sterilization, intrauterine devices, and implants). In women who are not able to or do not choose to use a highly effective method, a hormonal method may be acceptable.

- There are no data that suggest that retinoids transferred through semen result in teratogenic effects. (b) (4)

Pregnancy Testing
The initial pregnancy test should be done immediately prior to initiation of treatment.

Registry
Women who become pregnant while on palovarotene should be included in the Patient Registry.

Discussion at the Meeting:
Clementia asked for guidance as to when and how agreement is reached regarding the required key elements of a REMS vs Clementia's proposed approach. The FDA explained that the need for a REMS is evaluated during the NDA review. The Agency's intention is to notify an Applicant as soon as possible if a REMS will be necessary, and if so, the required elements. Risk management is also a discussion topic during the milestone communication meetings with the Applicant.

Clementia asked for clarification regarding the need for a post-approval study to assess palovarotene in human semen based on the recent discussion at the February 5, 2019, nonclinical teleconference. The FDA explained that the transfer issue discussed here is different from the testicular toxicity issue discussed at the nonclinical teleconference.

Question 15: ***The electronic Roche reports that were provided in the IND for FOP will also be included in the NDA; all other Roche studies will be cross-referenced to the Roche IND. Does the Division agree?***

FDA Response to Question 15:
No. All study reports and datasets should be included in the NDA.

The letter of cross-reference previously provided for IND (b) (4) is specific to a single protocol. A letter of cross-reference authorization that provides access to encompass all protocols and data generated from those studies should be provided in the NDA.

Discussion at the Meeting:
Clementia will provide pdf copies of the Roche legacy clinical study reports in addition to an updated letter of cross-reference authorization providing access to all information in the Roche IND for the planned NDA. The legacy study reports do not contain completed Case Report Forms (CRFs), therefore individual subject CRFs [e.g. for subjects with serious adverse events (SAEs) or who discontinue the study due to an AE] cannot be provided for the legacy studies. All safety data are included in the listings, and narratives for each of the relevant subjects are available and will be provided in the NDA.

Additional Clinical Pharmacology Comments:

- Method validation report and bioanalytical report for each bioanalytical method used in clinical pharmacology studies should be provided in the NDA. During method validation, stability evaluations should cover the expected sample conditions and storage duration before receipt at the analytical site (e.g., at the clinical site, during shipment, and at all other secondary sites) as well as during receipt and analysis at the analytical site.
- Plasma drug concentration data and pharmacokinetic parameter data should be submitted in xpt format.

Discussion at the Meeting:
Clementia acknowledged the additional clinical pharmacology comments.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See discussion above.

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan, and

it was concluded that the FDA will determine the need for a REMS during the review of the 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.

In addition, we note that a chemistry pre-submission meeting was held on February 7, 2019, and a nonclinical pre-submission meeting was held on February 5, 2019. We refer you to the minutes of those meetings for any additional agreements that may have been reached.

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* and *Pregnancy and Lactation Labeling Final Rule* 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Further discussion may be needed regarding the data to assess testicular toxicity and palovarotene in human semen.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	March 16, 2019

6.0 ATTACHMENTS AND HANDOUTS

FDA slides_Pre-NDA_CLIN_F2F_Fi.pdf

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/s/

THERESA E KEHOE
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120181

MEETING MINUTES

Clementia Pharmaceuticals, Inc.
Attention: Jeff Packman
275 Grove Street, Suite 2-400
Newton, MA 02466

Dear Mr. Packman:

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

We also refer to the teleconference between representatives of your firm and the FDA on February 5, 2019. The purpose of the meeting was to discuss the nonclinical data needed to support registration of palovarotene.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Mukesh Summan, Ph.D., DABT
Pharmacology and Toxicology Supervisor
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Breakthrough Therapy - Other

Meeting Date and Time: February 5, 2019, 11:00 A.M. to 12:00 P.M.
Meeting Location: Teleconference

Application Number: IND 120181
Product Name: Palovarotene

Indication: Prevention of heterotopic ossification in patients with Fibrodysplasia Ossificans Progressiva (FOP)

Sponsor/Applicant Name: Clementia Pharmaceuticals, Inc.

Meeting Chair: Mukesh Summan, Ph.D., DABT
Meeting Recorder: Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive and Urologic Products (DBRUP):
Audrey Gassman, M.D., Deputy Director
Theresa Kehoe, M.D., Medical Team Leader
Stephen Voss, M.D., Clinical Reviewer
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

EASTERN RESEARCH GROUP ATTENDEES

Kuang-Heng Hsiao
Sraavya Polisetti

SPONSOR ATTENDEES

Donna Grogan, Chief Medical Officer
(b) (4), Toxicology Expert Consultant
Isabelle Lemire, Director, Nonclinical Research
Jeff Packman, Chief Development Officer
Michael Harvey, Executive Director, Drug Development
Olivia Popescu, Senior Manager, Regulatory Affairs
Rose Marino, Medical Director

1.0 BACKGROUND

Fibrodysplasia Ossificans Progressiva (FOP) is a rare, chronic, painful, disabling, and fatal disease of abnormal bone formation. It is caused by a mutation in the bone morphogenetic protein (BMP) type I receptor ACVR1 (also known as ALK2) that leads to downstream activation of BMP bone-signaling pathways in the absence of BMP. Clementia is developing palovarotene for oral administration to prevent heterotopic ossification in patients with FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist.

Orphan drug designation for treatment of FOP was granted on July 21, 2014. Fast Track designation for prevention of heterotopic ossification following preosseous flare-ups in patients with FOP was granted on November 25, 2014. Breakthrough therapy designation was granted on July 11, 2017, for the prevention of heterotopic ossification (HO) in patients with FOP.

The FDA previously met with Clementia on October 23, 2018, to discuss the available data sufficient to support submission of a New Drug Application. At that meeting, FDA agreed that the available data would support filing of a marketing application for palovarotene for the prevention of heterotopic ossification associated with flare-up symptoms in patients with fibrodysplasia ossificans progressive (FOP). Clementia is now requesting a meeting to discuss the nonclinical data needed to support the initial registration of palovarotene.

FDA sent Preliminary Comments to Clementia on January 31, 2019.

2. DISCUSSION

General Comments

1. We note that you propose a different indication in your meeting package (treatment of fibrodysplasia ossificans progressiva) than the indication which received breakthrough therapy designation (prevention of heterotopic ossification (HO) in patients with fibrodysplasia ossificans progressiva). We recommend that you keep the indication language consistent with the breakthrough therapy designation as this is the indication for which we have been providing advice.
2. We note that the pre-NDA meeting has not occurred. Additional nonclinical studies may be required upon review of the pre-NDA meeting package.

Discussion at the Meeting:

There was no further discussion at the meeting.

Question 1a: ***Clementia believes that this package of nonclinical safety studies will adequately support the registration of palovarotene. Does the division agree?***

FDA Response to Question 1a:
No, we do not agree. Per the ICH S5(R3) guidance, conduct a nonclinical study evaluating female fertility. The adequacy of the nonclinical studies to support registration of palovarotene for the proposed indication will be a review issue.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 1b: ***Clementia plans to cross-reference Roche IND*** (b) (4) ***(which was filed in paper format) as part of its NDA submission. As agreed with the Division following the pre-IND meeting, Clementia provided electronic versions of reports for the 4-week study in rats, the 26-week repeat dose study in rats, and the 26/39-week repeat-dose study in dogs conducted by Roche (IND 120181, SN 0000, Module 4.2.3.2 Roche Study Reports 1007062, 1009627, and 1009654, respectively). These electronic reports will be included in the NDA, as well as electronic versions of the reports for both juvenile toxicology studies conducted by Clementia (IND 120181, SN 0020 Module 4.2.3.5.4,*** (b) (4) ***Study Reports 9000317 and 6700132). All other studies will be cross-referenced to the Roche IND. Does the Division agree?***

FDA Response to Question 1b:
Yes, this is acceptable for the NDA submission, provided that a more general letter of cross-reference authorization is provided for IND (b) (4) The letter of cross-reference previously provided is specific to a single protocol. Additionally, provide a complete list in your NDA submission of the nonclinical studies conducted for IND (b) (4) including their submission dates, that you intend to rely on to support the safety of palovarotene for the proposed indication. We prefer submission of electronic reports of all relevant studies.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 2: ***The results from nonclinical studies in several species with palovarotene or its metabolites indicate that palovarotene is not likely to adversely affect the function of the respiratory system. This conclusion is consistent with the results reported for other retinoids and is supported by the clinical safety data collected to date in healthy human volunteers, COPD subjects, and FOP subjects. In this context, Clementia does not believe that a safety pharmacology study evaluating potential effects on respiratory function in small groups of animals would provide additional meaningful safety information to patients or their caregivers, and hence does not intend to conduct a single-dose respiratory safety pharmacology study with palovarotene. Does the Division agree?***

FDA Response to Question 2:
Yes, we agree.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 3: ***Clementia believes that there is no benefit in conducting an embryofetal development study in pregnant animals of a second species because (a) palovarotene adversely affected fetal development when administered to pregnant rats; and (b) retinoids as a class are known to carry a risk of affecting fetal development. Accordingly, Clementia does not intend to conduct an embryofetal development study in a second species with palovarotene. Does the Division agree?***

FDA Response to Question 3:
Yes, we agree.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 4a: ***Clementia believes that given the extremely small patient population with FOP, palovarotene offers a meaningful benefit to patients and that the weight of evidence suggests that palovarotene does not pose a carcinogenic hazard to patients. Therefore, the company proposes not to conduct any study specifically to evaluate carcinogenic hazard.***

Does the Division agree that this approach is acceptable?

FDA Response to Question 4a:
Yes, this approach is acceptable for the proposed indication.

Discussion at the Meeting:
FDA clarified that this would also be acceptable for a proposed indication with a chronic treatment regimen.

Question 4b: ***Does the Division agree that the supporting information as summarized below is adequate to be included in the NDA in support of waiving this requirement?***

FDA Response to Question 4b:
The supporting information in your meeting package to justify waiving the requirement for an in vivo carcinogenicity study is adequate to be included in the NDA submission. In consultation with the Executive Carcinogenicity Assessment Committee (ECAC), a final assessment of the relevance of the supporting information regarding the carcinogenic potential of palovarotene and its value to support waiving the study requirement will be made during the NDA review cycle. The implications of the submitted information as well as other available information for product labeling will also be determined during the review cycle.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 5: ***Palovarotene adversely affected fetal development when administered to pregnant rats and also was positive for teratogenic potential in an in vitro embryonic stem cell assay. Therefore, women taking palovarotene will be advised to avoid becoming pregnant and to stop taking palovarotene if they do become pregnant. Clementia does not believe that a study to evaluate effects on fertility and early embryonic development in female animals would provide additional meaningful safety information to female patients or their caregivers. The proposed product label will carry the appropriate warnings regarding embryofetal risk. Clementia does not intend to conduct a study in female animals to evaluate the effects of palovarotene on female fertility or early embryonic development. Does the Division agree?***

FDA Response to Question 5:
No, we do not agree. The intended treatment population includes women of childbearing potential and the lack of information on the potential effects of palovarotene on female fertility and early embryonic development constitutes a gap in the palovarotene reproductive toxicology database. Therefore, conduct a nonclinical study to assess the effects of palovarotene on female fertility and early embryonic development. If effects are observed, evaluate the reversibility of these induced effects. Female animals should be dosed in this study according to regulatory guidelines for reproductive toxicity studies. The results of this study would provide valuable information for female patients, their partners, and caregivers regarding potential lasting effects of palovarotene on female fertility and early embryonic development. The available nonclinical information on the effects of palovarotene on embryofetal development in pregnant rats and on the in vitro teratogenic potential of palovarotene does not provide any information on potential fertility effects. The nonclinical fertility study may be conducted post-approval.

Regarding dose selection, the use of doses at or below the maximum tolerated dose (MTD) which are expected to yield AUC exposures below the human AUC at 20 mg/day is acceptable, because the study is intended to identify adverse effects on fertility and these effects may occur at these lower doses at which other clinically relevant toxicities have also been observed.

Discussion at the Meeting:
Clementia acknowledged the FDA's recommendations and intends to conduct the requested nonclinical fertility study as a post-marketing commitment. The FDA acknowledged the proposed study design on slide 5 and had no comments at the meeting. The FDA stated that they may provide additional feedback on the proposed design as a post-meeting comment. The FDA agreed to review a draft protocol submitted to the IND prior to initiation of the study. Clementia clarified that they intend to evaluate reversibility of effects observed in the study.

Post-meeting comment:
The design of the fertility and early embryonic development study on slide 5 appears to be adequate. If, based on the considerations described in the "Discussion at the Meeting" under Question 6, the study's objectives will include an evaluation of male fertility, male animals also need to be dosed for 4 weeks before mating with untreated females.

Question 6: ***The palovarotene nonclinical toxicology package will not include a study evaluating the potential effects on fertility and reproductive function in male animals. Palovarotene has been shown to cause testicular toxicity at 5 mg/kg (Roche Study Report 1007062 - IND 120181, SN 0000, Module 4.2.3.2), which corresponds to exposures that are clinically relevant during flare-up dosing in humans. It is noted that this dose exceeds the MTD levels in rats and thus testicular toxicity may not be a direct drug effect. The proposed product label will clearly describe these effects. Does the Division agree?***

FDA Response to Question 6:
Yes, we agree. A study evaluating fertility and reproductive function in male animals is not needed. However, the effects on sperm parameters from the 28-day rat study need to be included in labeling. In addition, a clinical assessment of human male sperm characteristics is required.

Discussion at the Meeting:
Clementia explained that dosing of healthy volunteers with palovarotene (20 mg/10 mg) in order to obtain semen samples for the determination of sperm characteristics would not be possible due to tolerability issues, and that the study is also not feasible in male FOP patients due to restrictions in mobility. Clementia proposed to address fertility in the labeling by including sperm results from the 28-day rat study (b) (4) The FDA asked for clarification regarding tolerability issues. Clementia stated that there is a concern about risk without benefit for healthy subjects based on the mucocutaneous side effects of palovarotene. The FDA explained that their concern is based on the decreases in sperm counts and motility noted in the 28-day rat study and nonclinical data from other compounds in this class (retinoids). The FDA suggested an (b) (4) option of including male animals in the post-marketing rat fertility study to assess effects on male fertility. The FDA also asked Clementia to seriously consider the best approach (e.g. animal model or verses human study) to address the concern, considering the needs of the patient population.

Question 7: ***Clementia has evaluated the potential risk of male-mediated developmental toxicity as described in draft guidance document entitled "Assessment of Male-Mediated Developmental Risk for Pharmaceuticals" and concluded that the risk is extremely low. Does the Division agree that this analysis adequately addresses this issue?***

FDA Response to Question 7:
We agree that the risk for male-mediated developmental toxicity is low. However, a clinical evaluation of palovarotene concentrations in human male semen is required.

Discussion at the Meeting:
See Discussion under Question 6. The FDA explained the concentration and clearance of the drug in semen is important to address in the patient population, especially with consideration of chronic therapy.

Question 8: ***Clementia understands the recent requirement regarding the inclusion of nonclinical data in the Standard for Exchange of Nonclinical Data (SEND) format applies to studies that started after December 2016. Since all nonclinical studies in support of registration of palovarotene (including Roche legacy studies), were performed prior to December 2016, and Clementia has no access to study databases, datasets for these studies are not planned to be provided; those study reports that will be included in the NDA as per Question 1(b) will be provided in editable pdf format. Does the Division agree this approach is acceptable?***

FDA Response to Question 8:
Yes, we agree.

Discussion at the Meeting:
There was no further discussion at the meeting.

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* and *Pregnancy and Lactation Labeling Final Rule* 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Clementia will submit the protocol for a nonclinical study to assess the effects of palovarotene on female fertility and early embryonic development for FDA review prior to initiation. Further discussion regarding how to address sperm/semen assessment will be needed.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	March 7, 2019

6.0 ATTACHMENTS AND HANDOUTS

IND 120181 FDA slides_NONCLIN_TC_final_.pdf

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/s/

MUKESH SUMMAN
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CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 120181
Request Receipt Date	5/18/17
Product	Palovarotene oral capsules
Indication	Treatment of Fibrodysplasia Ossificans Progressiva (FOP)
Drug Class/Mechanism of Action	Retinoic acid receptor gamma (RARγ) agonist
Sponsor	Clementia Pharmaceuticals, Inc.
ODE/Division	ODE III/ DBRUP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	7/18/17

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Palovarotene is indicated for prevention of heterotopic ossification in patients with Fibrodysplasia Ossificans Progressiva (FOP).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Fibrodysplasia Ossificans Progressiva (FOP) is a rare disease (~800 confirmed cases globally). FOP is caused by a mutation in the bone morphogenetic protein (BMP) type I receptor, or activin A receptor type I (ACVR1), leading to constitutive activation of BMP bone-signaling pathways in the absence of BMP. Beginning in early childhood, patients with FOP develop extraskeletal bone formation in muscles, tendons and ligaments known as heterotopic ossification (HO). Formation of HO generally occurs following "flare-ups", which are episodes of painful localized soft tissue swelling that occur at an average per patient of ~2 per year and resolve in a period of weeks to months, often leaving a permanent residuum of HO. Some flare-up episodes occur following local trauma, while others appear spontaneous. The triggering factor(s) for subsequent HO formation are not well understood. It is believed that HO formation may also occur insidiously, apart from acute flare-ups. The progressive, lifelong accumulation of HO in segments, sheets and ribbons of extra bone, especially across joints, causes restriction of movement, deformities and severe disability. Complications may include chest wall deformity (thoracic insufficiency syndrome); ankylosis of the temporomandibular joints resulting in severe tooth decay and malnutrition; or localized skin breakdown. Most

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

patients are confined to a wheelchair by their 20s due to ossification around the hips. Survival is shortened (median 56 years), most often by cardio-respiratory failure and pneumonia. There is no effective treatment.

Palovarotene is an orally available retinoid that was initially developed by Roche (b) (4) , and all data were transferred to the current sponsor, Clementia Pharmaceuticals. Clementia is developing the drug for the prevention of HO in adults and children with FOP (IND 120181 was opened 4/28/14). Orphan drug and fast track designations for FOP were granted in 2014. RARγ agonists such as palovarotene inhibit the downstream effectors of the mutated ACVR1 gene, causing interruption of the BMP signaling pathway. This diverts mesenchymal stem cells away from chondrogenesis, potentially preventing the subsequent endochondral bone formation. Various animal models of HO demonstrated that palovarotene caused dose-dependent reductions in new HO.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Prior to the palovarotene development program, there were no systematic prospective studies of FOP, and the appropriate endpoints to document disease progression were uncertain. The sponsor's initial studies in treated and untreated patients showed that about half of flare-ups resulted in the formation of new HO, which could be detected and quantified by CT scan within 12 weeks of flare-up onset (plain x-rays, and evaluations at 6 weeks were not sufficiently sensitive). Preliminary data showed that palovarotene treatment may reduce the incidence of, and especially the volume of, new HO following flare-ups. Based on the data available, the Division accepts heterotopic ossification as determined by CT scan as a primary endpoint.

The Sponsor also evaluated the following secondary clinical endpoints in the trials:

- The Cumulative Analogue Joint Involvement Scale (CAJIS) was developed by the sponsor for FOP as an objective measure of joint mobility. The investigator assesses range of motion at each of 12 joints (bilateral shoulder, elbow, wrist, hip, knee, and ankle) and 3 regions (cervical-spine, thoracic-/lumbar-spine, jaw), grading each as 0 (normal), 1 (limited movement) or 2 (functionally ankylosed), for a total score of 0-30.
- Range of motion by goniometer at flare-up sites (early studies).
- The FOP-Physical Function Questionnaire (FOP-PFQ), developed by the sponsor for FOP, includes questions about activites of daily living and physical performance.
- The Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scale assesses general health.

Cross-sectional analyses of baseline data showed significant correlations between CAJIS or FOP-PFQ with total body burden of HO (volume in mm^3, or number of body regions involved, by whole body CT). Increasing age also correlated significantly with each of these measures (CAJIS, FOP-PFQ and total burden of HO). However, changes in the functional and patient-reported measures listed above, over the 12-week course of a flare-up, did not correlate significantly with subsequent formation of HO, and did not differ between treated and untreated episodes. Although the cross-sectional data suggest that these are clinically relevant measures, the Division believes they are not useful endpoints in the relatively short time frame of the trials.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

Despite the lack of correlation with clinical outcomes in the clinical studies of short duration, the Division believes that HO is the central feature of FOP and is the basis of the clinical manifestations. Detection of HO by CT scan is sensitive to change in the time frame of clinical studies while other functional endpoints are not. Therefore, DBRUP agrees with the Sponsor that new HO volume as detected by whole body CT scan is acceptable as the primary efficacy endpoint for Phase 3. DBRUP considers this endpoint to be clinically relevant and adequate to support full approval rather than accelerated approval. The percentage of patients with new HO will be used as a secondary endpoint, and the functional outcomes (CAJIS, FOP-PFQ, PROMIS) will be included as exploratory endpoints.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Another biomarker that is likely to predict clinical benefit is detection of osteogenic activity via ^{99m}Tc isotope bone scan, which has been used in FOP patients to demonstrate uptake in areas of HO. Additionally, ^{18}F-NaF PET is a modality that is used clinically to monitor various bone disorders, providing a quantitative measure of bone mineralization. Prevention of new HO, documented by ^{18}F-NaF PET with volumetric CT, is under evaluation by a different sponsor as an endpoint for HO in patients with FOP. Although ^{18}F-NaF is not taken up by mature bone tissue, it may be acceptable to evaluate new HO lesions in FOP.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

There is no approved or effective therapy for FOP. Flare-ups are often treated with high dose glucocorticoids or NSAIDs to alleviate symptoms, but there is no evidence that this prevents HO formation. Opioids are frequently required to control severe pain. Surgery to remove heterotopic bone has been reported to be ineffective and to provoke more severe HO development, and is therefore contraindicated.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Regeneron Pharmaceuticals is investigating another potential FOP treatment: REGN2477, a monoclonal antibody that binds activin A (IND 130595). REGN2477 inhibited new HO formation in a murine model of FOP, and was thereby granted Fast Track designation on 6/5/17. There are no clinical data yet available involving REGN2477 treatment of FOP, therefore breakthrough therapy designation would not be applicable, (b) (4). DBRUP is not aware of any other drugs under development for the treatment of FOP.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

This BTD request is based on data from two phase 2 studies: an initial randomized, controlled trial (study PVO-1A-201) and open label extension (study PVO-1A-202). Study 201 and Part A of study 202 evaluated episodic treatment of

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

acute FOP flare-ups for 6 weeks, in patients ≥6 years years old. Subsequently, new animal data suggested a benefit from continuous treatment and higher dose treatment of flare-ups. Therefore the currently ongoing Part B of study 202 is evaluating chronic dosing in adult FOP patients, as well as treatment of flare-ups (adults or children) at a higher dose regimen for 12 weeks. A prospective natural history study (NHS, study 001) is being conducted concurrently.

Palovarotene clinical trials in FOP patients

Study ID	Phase	Study design	Treatment groups (daily doses)	N enrolled	# of patients with flare-ups/ total # of flare-ups	Endpoints
PVO-1A-201	2	Treatment of flare-ups Double blind, randomized placebo controlled, multicenter, dose finding, proof of concept	10 mg/5 mg*	21	21/ 21	New HO at flare-up site (x-ray, CT) Edema/swelling (MRI, ultrasound) Range of motion Patient-reported pain/ swelling, FOP-PFQ, PROMIS Biomarkers of cartilage/ bone metabolism, angiogenesis, inflammation
			5 mg/2.5 mg*	9	9/ 9	
			Placebo	10	10/10	
PVO-1A-202	2	Open label extension <u>Part A</u>: Treatment of flare-ups during an additional 12 months Complete	10 mg/5 mg*	40 (all study 201 patients)	20/ 28	
		<u>Part B</u>: Chronic + flare-up dosing Up to 24 months Ongoing	Chronic dose: 5 mg (adults) Flare-ups: 20 mg/10 mg**	50 (32 from 202 Part A, 18 new)	17/ 19	
PVO-1A-001	0	Natural history study Multicenter Prospective, 3 year observation, ongoing	No intervention	114	14/ 18	Similar to phase 2 assessment of flare-ups, and annual measures

*10 5 mg and 5/2.5 mg regimens: initial dose for 2 weeks, subsequent dose for 4 weeks (total 6 weeks); for children 6-14 y/o, weight-based dosing reduction
** 20/10 mg regimen: 20 mg for 4 weeks, then 10 mg for 8 weeks (total 12 weeks); children (<90% skeletally mature) received weight-based equivalent of 20/10 mg at flare-ups only (no chronic dosing)

The 40 FOP patients in study #201 had a mean age of 21.3 years (range 7-53). The 114 NHS patients (study #001) had a mean age of 17.6 years (range 4-56). The age difference may be due to the study #201 entry criteria, which initially required age ≥15 years. The mean age at first flare-up was similar (~5 y/o) between patients in the two studies. The gender distribution was also similar (45% male in study 201, 54% in NHS). All patients had extensive HO in multiple body regions, with the most common locations at cervical spine, shoulder and upper back (each >90% of patients).

In preliminary data from study 202 Part B, flare-ups have occurred in 8 “skeletally immature” patients (mean age 14 yr, range 7-34) and in 9 “skeletally mature” patients (mean age 27 yr, range 15-45).

Patients with flare-ups in #201, #202 and NHS studies were assessed at week 12 of the flare-up for new HO formation by CT (and also x-ray initially), and for the presence of soft tissue edema by MRI or ultrasound (US). In addition to flare-up assessments, yearly CT is conducted in Part B of study #202 and in the NHS. Images were evaluated for HO (treatment-blinded) by two independent procedures:

- Primary Read process, in which images in each modality (x-ray, CT, MRI/US) were evaluated independently, e.g. x-rays were evaluated for HO without reference to the patient’s CT or MRI
- Global Read process, in which new HO was assessed only after full evaluation of all images across modalities and time points

Interpretations from these two methods (presence or absence of new HO) were discordant in 13% of flare-ups. Upon

evaluation, the sponsor concluded that the data from multiple modalities in the Global Read process leads to more accurate assessments of HO.

To date, the phase 2 and NHS studies have generated 12-week outcome data on a total of 103 flare-ups. The most common flare-up sites are the hips, knees and upper back. The table below shows the number of flare-up episodes, and the proportion of these episodes that resulted in formation of new HO detectable by CT at week 12, in patients pooled as follows:

- Placebo recipients (study 201) + Untreated patients (NHS)
- All PVO 10/5 mg recipients (studies 201 + 202 Part A)
- Study 202 Part B:
    - Flare-up only (skeletally immature)
    - Chronic/flare-up (skeletally mature)

(Not included in this table are flare-ups in 9 patients in study 201 who received the lowest dose regimen, 5/2.5 mg.)

Table 5. Proportion of Flare-Ups with New HO by CT at Week 12 from the Pooled Studies and Study PVO-1A-202/Part B

	Placebo/Untreated	All PVO 10/5 mg	PVO 20/10 mg	
			Flare-Up Only	Chronic/Flare-Up
	N=28 n/N' (%)	N=40 n/N' (%)	N=9 n/N' (%)	N=10 n/N' (%)
Primary Read	8/28 (28.6)	14/48 (29.2)[1]	4/9 (44.4)	2/10 (20.0)
Global Read	12/28 (42.9)	11/47 (23.4)[1,2]	NA	NA

[1] Excludes one flare-up from a subject in the palovarotene 10/5 mg group in Study PVO-1A-201 who was less than 80% compliant with study medication (subject was 60% compliant).

[2] The Global Read review excludes one flare-up from a subject in Study PVO-1A-202/Part A with non-evaluable results at Week 12.

Percent calculated as n/N' x 100, where N' is the number of flare-ups with interpretable outcomes.

Note: analyses include results obtain by x-ray for those without available CT scan. Only Primary Read results are currently available for Study PVO-1A-202/Part B (NA=not available).

According to the Global Read process, the proportion of flare-ups with new HO was lower with palovarotene 10/5 mg treatment than with placebo/untreated: 23.4% vs. 42.9%. The proportion was lower with the chronic/flare-up regimen (20%), but the number of episodes was low. Analysis of the volume of new HO, for those flare-ups with new HO (table below), also shows trends of less new HO with palovarotene compared to placebo/untreated, especially in the chronic/flare-up group (though with only 2 episodes in this group).

Table 7. Volume of New HO (in Flare-Ups with New HO) by CT at Flare-up Week 12 in the Pooled Studies

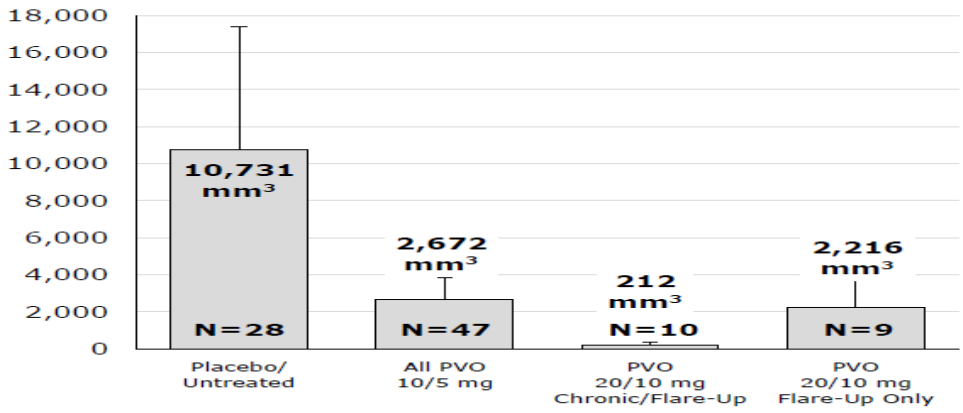
	Placebo/Untreated	All PVO 10/5 mg	PVO 20/10 mg	
	N=12	N=11	Flare-Up Only N=4	Chronic/Flare-Up N=2
Primary Read[1]	n=7	n=11	n=2	n=2
Mean (SD)	42,922 (63,382)	11,416 (13,306)	9,974 (1,488)	1,061 (4.5)
Flare-up locations	3 hips 1 each: knee, neck, back, arm	5 hips 3 knees 1 each: distal lower extremity, shoulder, lower spine/abdomen	2 hips	1 each: hip, shoulder

[1] HO volumes were calculated from CT scans during the Primary Read process. Therefore, values for Study PVO-1A-201 do not include one subject in the placebo group and two subjects in the palovarotene 5/2.5 mg group identified with new HO on the Global Reads, and exclude the volume (61.5 mm^3) observed on the Primary Reads from one subject in the palovarotene 10/5 mg group that was deemed not to be new HO on the Global Reads. No volume assessment is available for one subject in Study PVO-1A-202/Part A whose Week 12 Global Read assessment was indeterminate or for the four untreated flare-ups in the NHS with new HO identified by Global Reads. In addition, the volume for two flare-ups in Study PVO-1A-202/Part B Flare-Up Only regimen was not evaluable as a segment of the HO was outside the field of view; and volume was incomplete for one flare-up in Study PVO-1A-202/Part B Flare-Up Only dosing as a segment of one of the new HO lesions was outside the field of view.

Source: EOP2 meeting briefing document

The above table includes only the volume of new HO for those flare-ups with new HO. The figure below represents mean volume of new HO for all flare-ups in the pooled studies (volume=0 for flare-ups without new HO).

Volume of New HO at Week 12 for All Flare-Ups from the Pooled Studies and Study PVO-1A-202/Part B by Dosing Regimen



Placebo/Untreated: placebo-treated subjects in Study PVO-1A-201 and untreated subjects in the NHS.
All PVO 10/5 mg: subjects administered 10/5 mg palovarotene in Studies PVO-1A-201 and PVO-1A-202/Part A.
PVO 20/10 mg Chronic/Flare-Up: subjects in Study PVO-1A-202/Part B who received chronic palovarotene (5 mg) daily and 20/10 mg palovarotene for a flare-up.
PVO 20/10 mg Flare-Up Only: subjects in Study PVO-1A-202/Part B who did not receive chronic palovarotene (5 mg) daily; these subjects only received 20/10 mg palovarotene for a flare-up.
Note: N equals the number of flare-ups.

Unlike the measures of new HO, changes in functional measures and PROs (range of motion at flare-up site, FOP-PFQ and PROMIS Global Health Scale) were not significantly different between palovarotene and placebo/untreated groups, or between flare-ups with vs. without new HO. The sponsor concludes that although these are clinically relevant measures, they are not sufficiently sensitive to detect treatment effects over the 12 week course of a flare-up.

b. Include any additional relevant information.

The data regarding incidence and volume of new HO formation during FOP flare-ups are limited based on the small number of available patients, but do appear to provide preliminary clinical evidence of a treatment effect that may represent substantial improvement over current clinical practice, i.e. the absence of effective therapy.

During the initial development of palovarotene (b) (4), Roche conducted multiple studies with a total of >200 healthy subjects and >600 (b) (4) patients, the latter including >450 patients who received 5 mg palovarotene for 2 years. The resulting safety data showed that palovarotene is associated with retinoid class adverse effects, most commonly mucocutaneous symptoms (e.g. rash, dry skin, dry mouth, cheilitis). Other retinoid effects may include chondrodysplasia, premature epiphyseal closure, enthesopathy, hypertriglyceridemia, pancreatitis, teratogenicity, pseudotumor cerebri. and psychiatric disorders including suicide.

The Sponsor is now moving to a regimen of chronic therapy for the Phase 3 trial, and growth in pediatric patients is the predominant concern. Close monitoring of growth in skeletally immature patients is included in the Phase 3 trial.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

FOP is a serious and severely disabling disease, and no effective treatment is currently available. The irreversible accumulation of HO is the underlying cause of FOP clinical manifestations and, based on data in this sponsor's natural history study, correlates with indices of functional impairment. Therefore, DBRUP agreed with the sponsor at a recent meeting that new HO is a clinically meaningful outcome and an appropriate primary endpoint. Although data are preliminary and limited by the small number of patients available, the phase 2 studies show that palovarotene treatment of episodic FOP flare-ups appears to reduce the subsequent incidence of new HO, especially the volume of new HO as measured by whole body CT scan, in comparison to patients given placebo or untreated in the natural history study. This constitutes preliminary evidence that palovarotene may demonstrate substantial improvement over available therapy on important outcomes, thus fulfilling the criteria for breakthrough therapy designation.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

- If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor submitted a phase 3 protocol synopsis which will be discussed at an end of phase 2 meeting on 6/27/17. The Phase 3 protocol is proposed as a single arm, open label study of palovarotene treatment of FOP in patients age ≥4 years. Dosing will be similar to the phase 2 study #202 Part B, with chronic maintenance dosing of 5 mg supplemented by high dose treatment of flare ups (20 mg x 4 weeks then 10 mg x 8 weeks). Comparison data will be provided by the ongoing natural history study, which has similar enrollment criteria and outcome assessments. The primary endpoint will be the annualized volume of new HO. Because of the change in treatment approach (chronic therapy plus flare-based dose escalation in Phase 3 vs. flare-only therapy in Phase 2), DBRUP believes that the Phase 3 trial data are necessary to support the proposed indication. DBRUP will continue to work with the sponsor to facilitate expedited development for a potential FOP indication.

- If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

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

/s/

STEPHEN R VOSS
07/12/2017

THERESA E KEHOE
07/12/2017

HYLTON V JOFFE
07/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120181

MEETING MINUTES

Clementia Pharmaceuticals, Inc.
Attention: Michael D. Harvey, Ph.D.
Executive Director, Drug Development
4150 Sainte-Catherine Street West, Suite 550
Montreal, Quebec Canada H3Z 2Y5

Dear Dr. Harvey:

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

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2017. The purpose of the meeting was to discuss a Phase 3 clinical study design.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2, Pre-NDA
Meeting Date and Time:	June 27, 2017, 11:00 A.M. to 12:00 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 120181
Product Name:	Palovarotene
Indication:	Treatment of Fibrodysplasia Ossificans Progressiva (FOP)
Sponsor/Applicant Name:	Clementia Pharmaceuticals Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive and Urologic Products (DBRUP):
Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Medical Team Leader
Stephen Voss, M.D., Clinical Reviewer
Jacqueline Karp, M.D., Medical Officer
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Peng Zou, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III
Jeffry Florian, Ph.D., Pharmacometrics Team Leader, Division of Pharmacometrics

OTS, Office of Biostatistics, Division of Biometrics III:
Kate Dwyer, Ph.D., Biometrics Reviewer
Mahboob Sobhan, Team Leader

Office of Pharmaceutical Quality (OPQ)
Mark Seggel, Ph.D., Application Technical Lead, Office of New Drug Products (ONDP)

Office of New Drugs, Immediate Office, Rare Diseases Program:
Kathryn O'Connell, M.D., Ph.D., Medical Officer

Office of New Drugs, Immediate Office, Clinical Outcome Assessments Staff:
Jing (Julia) Ju, M.D., Reviewer
Selena Daniels, Pharm.D., M.S., Team Lead

Office of New Drugs, Division of Pediatric and Maternal Health:
Ethan Hausman, M.D., Medical Officer
Hari Sachs, M.D., Lead Medical Officer
John Alexander, M.D., Deputy Director

SPONSOR ATTENDEES
Clarissa Desjardins, Ph.D., Chief Executive Officer
Donna Grogan, M.D., Chief Medical Officer
Jeff Packman, M.B.A., Chief Development Officer
Michael Harvey, Ph.D., Executive Director Drug Development
Stephen Lake, Sc.D., Vice President, Biostatistics and Data Management
Fei Shih, M.D., Ph.D., Executive Medical Director

1.0 BACKGROUND

Fibrodysplasia Ossificans Progressiva (FOP) is a rare, chronic, painful, disabling, and fatal disease of abnormal bone formation. It is caused by a mutation in the bone morphogenetic protein (BMP) type I receptor ACVR1 (also known as ALK2) that leads to downstream activation of BMP bone-signaling pathways in the absence of BMP. Clementia is developing palovarotene for oral administration to treat FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective retinoid.

Orphan drug designation for treatment of FOP was granted on July 21, 2014. Fast Track designation for prevention of heterotopic ossification following preosseous flare-ups in patients with FOP was granted on November 25, 2014. A preliminary breakthrough advice teleconference occurred on November 16, 2016.

The FDA met with Clementia on March 1, 2017, to discuss the data from their Natural History Study (NHS) and Phase 2 studies to obtain guidance regarding design of their Phase 3 program.

The purpose of this End of Phase 2 meeting is to obtain feedback from the Division regarding the remaining aspects of Clementia's Phase 3 clinical study (the MOVE trial) which has been designed to support full approval of palovarotene for the treatment of FOP.

FDA sent Preliminary Comments to Clementia on June 22, 2017.

2. DISCUSSION

Question 1: ***The Natural History Study (PVO-1A-001, NHS) has generated the largest prospectively obtained, protocol-driven dataset in FOP, with baseline data from 114 subjects (approximately 14% of the world's known patients). In addition, follow-up data is expected from approximately 90 subjects at Month 12 and approximately 45 subjects at Month 24 by the end of 2017. Given the similarities in the inclusion and exclusion criteria, consistency of standard of care world-wide, similarity of follow-up observation period, and the standard process of obtaining and analyzing the objective primary endpoint (new HO by WBCT scan), Clementia proposes that the NHS meets the criteria for use as the control group to be used in the primary efficacy analysis of the Phase 3 MOVE study.***

Does the Division concur that the NHS meets the criteria for use as the control group in the primary efficacy analysis?

FDA Response to Question 1:
The natural history study (NHS) may be acceptable to provide patients to serve as an external control group (historical control). The acceptability of NHS data and comparability of NHS and phase 3 patients will be NDA review issues. The FDA continues to believe that randomized control data are preferred, are not necessarily infeasible, and could provide more convincing evidence of efficacy, particularly if the treatment effect turns out not to be large. In addition, we have concerns that the lack of a randomized control may impair the safety evaluation of your product because the NHS and your proposed trial are not assessing safety in the same way.

We agree with the provisions for treatment blinding of heterotopic ossification (HO) assessments by whole body computed tomography (WBCT) scans.

Every effort should be made to ensure comparability between assessment methods used in clinical trials with the natural history control to allow meaningful comparison of changes over time.

Discussion at the Meeting:
Clementia explained they have considered several different study designs and what key factors were considered (see Slide 5). Clementia presented sample size calculations in which they concluded that a substantial increase in sample size would be required for a randomized trial design, making this not feasible in their view (Slide 6). FDA asked for clarification of what assumptions were used in calculating the sample size. Clementia replied that annualized HO volume was used as the primary endpoint and 30% reduction in probability of having any new HO and 50% reduction of new HO volume in subjects with new HO in one year.

Clementia summarized the annual safety assessments included in the NHS (Slide 8) and concluded that although the collection of adverse events is limited to study-related procedures, the evaluation of the objective measures allows for comparison with data to be collected in the MOVE study. The FDA recommended that Clementia include these details in the safety comparison discussion in the clinical study report.

Clementia will have 45 patients with 2 years of Patient-Reported Outcome (PRO) data from the NHS at the end of 2017. The FDA stated it will be important to review this data in support of the clinical outcomes associated with palovarotene. While the outcomes in the 12 week trials may not be informative, the clinical patient reported outcomes at 2 years should provide additional support.

Clementia estimates 50 patients will transition from the NHS to the MOVE trial.

Question 2: ***The Phase 3 MOVE trial is designed to evaluate the efficacy and safety of palovarotene in reducing new HO volume (as assessed by WBCT scan) in subjects with FOP and maximally utilizing the data obtained in the NHS (described above). As such, key inclusion and exclusion criteria were designed to correspond to those from the NHS.***

Are the chosen criteria, including the lower age limit of 4 years old, acceptable to the Division for the enrollment of subjects in the Phase 3 registration trial?

FDA Response to Question 2:
The inclusion and exclusion criteria are generally acceptable. We recommend that you submit the complete study protocol and statistical analysis plan for review, comment, and agreement prior to study initiation.

The body weight-based regression analysis of adult pharmacokinetic (PK) parameters may not be able to accurately predict pediatric pharmacokinetic parameters. We recommend that pharmacokinetic data from pediatric patients in Study PVO-lA-201 and Study PVO-1A-202 be used to validate the predicted pediatric PK parameters and confirm the proposed weight-adjusted pediatric doses.

Discussion at the Meeting:
Clementia proposed to commence study initiation in parallel with submission of the Phase 3 protocol. The FDA agreed, but reminded Clementia the FDA may have additional comments. Clementia intends to submit an abbreviated statistical analysis plan (SAP) because full details regarding the planned statistical analysis are being finalized. The FDA stated that the SAP should be submitted as early as possible in Phase 3 for our review. The FDA suggested that Clementia also consider submitting a Target Product Profile.

See Discussion under Questions 4 and 6 regarding endpoint and PK assessments.

Question 3: ***There will be two sources of subjects eligible for enrollment in the Phase 3 MOVE trial:***
(1) subjects from the NHS; and (2) new subjects who have not participated in any previous Clementia-sponsored study. Subjects from these two sources will comprise the palovarotene treatment group used for comparison to the NHS control group.

Does the Division concur with this approach?

FDA Response to Question 3:
This is acceptable if you are to proceed with the NHS approach. However, allowing NHS patients to enroll in the phase 3 study could create bias. Documentation of the reasons given for such enrollment may become important in interpretation of the data. Also see our response to Question 1 about our preference for a randomized trial.

Discussion at the Meeting:
See Discussion under Questions 1 and 6.

Question 4: The dosing regimen proposed for the Phase 3 study was based on the animal pharmacology data, Phase 2 and NHS flare up results. The animal pharmacology data demonstrate a dose-related decrease in new HO volume, with similar results in the clinical program. Although the data are preliminary, it is proposed that the best results have been obtained when the 5-mg palovarotene dose is administered once daily chronically, with dose escalation at the time of a flare-up to 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (chronic/flare-up regimen; with equivalent weight-based dosing in skeletally immature children). The formation of new HO is irreversible, and the cumulative disability is permanent. Because the risks of under treatment are very high, FOP should be treated aggressively in order to evaluate the maximal potential treatment benefit, while carefully monitoring for any potential safety concerns.

Does the Division concur that this chronic/flare-up regimen can be used for all subjects enrolled in the trial, including skeletally immature children, for whom dose strengths will be based on body weight?

FDA Response to Question 4:
The chronic dosing (5 mg daily for up to 24 months) for adult patients appears reasonable. In study 202B, the flare-up dosing regimen (20 mg for 28 days followed by 10 mg for 56 days) was associated with 20% subjects requiring dose de-escalation. The Phase 3 protocol should have clear criteria, schedule, and algorithms for dose interruption and dose de-escalation.

Justify the proposed weight-based dose adjustment for the pediatric population (refer to our response to Question 2). You should submit available pediatric PK data (including individual PK data and body weight) to demonstrate that equivalent exposure of palovarotene was achieved in pediatric patients using the proposed weight-adjusted doses and adult patients.

A chronic dosing regimen in the pediatric population, especially skeletally immature children, is of concern. We recommend stringent safety monitoring, as outlined in our response to Question 5.

Discussion at the Meeting:
Clementia presented the protocol specified dose de-escalation rules (Slide 19).

Clementia summarized the pharmacokinetic characteristics of palovarotene (Slide 10). Clementia presented the observed vs. predicted area under the curve (AUC) ratio of individual subjects enrolled in Study 201 and Study 202B (Slide 11) to support the proposed linear regression model used to estimate weight-adjusted doses. The FDA stated that the AUC ratio between pediatric subjects and adult subjects is important and asked Clementia to provide individual body weight and raw PK data, including clearance values. Clementia agreed to provide the requested data.

Question 5: ***Palovarotene has a well described safety profile following chronic administration of 5 mg once daily for up to 2 years in adults, and episodic treatment for 12 weeks in adults and children. It is recognized that the doses currently under evaluation in the clinic, and proposed for the Phase 3 study, are higher than the NOAEL observed in the adult and juvenile toxicology studies. However, the clinical data obtained to date have demonstrated no specific safety concerns, suggesting that the potential benefit of inhibiting new HO formation outweighs the potential risks with the proposed regimen. There is a dose-related increase in mucocutaneous adverse events that are tolerated with the use of prophylactic treatments and/or dose reductions. There are no significant changes in laboratory safety parameters or electrocardiograms. Preliminary data have not revealed any adverse effects on epiphyseal growth plate or linear/knee height in children following episodic treatment, supporting the evaluation of chronic dosing in children at a 5-mg weight-based equivalent dose. Safety monitoring procedures will continue to evaluate or any potential adverse effect on growth plate and linear growth.***

Does the Division concur with the proposed safety monitoring procedures, including surveillance for potential growth effects in children?

FDA Response to Question 5:
A concern regarding treatment-emergent suicidal ideation and behavior exists for retinoid products. The Columbia-Suicide Severity Rating Scale (C-SSRS) should be conducted at every visit, with specific criteria for drug discontinuation and further evaluation/referral. We refer you to Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.

In the pediatric population, evaluation of growth will be important. The Phase 3 protocol should clearly define and standardize the procedures to be used for both linear height by stadiometer and knee height. Clarify if you intend to calculate Z-scores for both linear height and knee height.

Discussion at the Meeting:
Clementia plans to assess C-SSRS at every 3-month safety visit and at the monthly flare-up assessments.

Clementia will assess linear and knee height in triplicate every 6-months. Clementia explained that normative data will be used to assess linear height, however, they are unsure if z-score can be calculated due to the spinal deformity often seen in subjects with FOP.

Pediatric normative data is not currently available for knee height. The FDA would be interested in data demonstrating at what age height is affected based on disease progression.

Question 6: ***With the NHS as the control group, the primary efficacy analysis will use a linear mixed effects model to account for the within-patient correlation and will adjust for baseline covariates (eg, age, baseline whole body HO volume).***

Does the Division concur with the statistical approach proposed?

FDA Response to Question 6:
We continue to have concerns with new HO volume as the sole endpoint for assessment of HO. For example, the clinical relevance of new HO formation may depend on the site of occurrence, and it is unclear whether new HO at a site with existing HO would have similar clinical relevance to new HO at an unaffected site. We recommend additional secondary endpoints that assess these scenarios and other secondary endpoints such as the proportion of subjects with new HO. The number of body regions with HO should also be described. Additionally, an endpoint for the proportion of subjects with flare-ups should be included and the number of flare-ups per subject should be described.

In addition, it is unclear how you intend to calculate annualized change in HO, and how you intend to compare Phase 3 interim data at month 18 with data from the NHS that are assessed annually.

We concur with the mixed effect model approach. However, we need more details on how you plan to address the concern for bias mentioned in our response to Question 3. In addition, clarify the interim threshold for declaring efficacy based on percent reduction in HO rather than change in HO. You may also consider a propensity score analysis if comparability is an issue.

Discussion at the Meeting:
Clementia plans to include additional secondary endpoints: proportion of subjects with any new HO, change in number of body regions with any HO, proportion of subjects reporting any flare-ups, and flare-up rate per patient month exposure.

Clementia explained their analysis of annualized change in HO (Slide 14), how they plan to account for potential bias (Slide 15), and their sensitivity analysis plan (Slide 16). Clementia also explained their interim analysis plan (Slide 17). The FDA asked Clementia whether they thought about using an indicator variable for duration of exposure in the model rather than an annualized change in HO as the primary efficacy. FDA asked Clementia to provide more specifics on the time-weighting of the model, and to include more sensitivity type analyses in their SAP. Clementia clarified that the interim analysis is to occur when 35 subjects complete 1 year and every 6 months thereafter. The FDA also asked what they would consider as key secondary endpoints. Clementia replied that they have not thought about key secondary endpoints. FDA advised Clementia to consider key secondary endpoints and to pre-specify the endpoints in the protocol and SAP.

Additional Comments:

1. In your summary table of clinical studies related to the chronic obstructive pulmonary disease (COPD) and FOP programs, provide information on the drug product formulations used in the clinical studies. If the formulation used in pivotal pharmacokinetic studies is different from the to-be-marketed formulation, explain your plans to bridge them.

2. It appears that a food effect study (Study RB16327) was conducted in a small number of subjects in the COPD program. We recommend that a food effect study be conducted during development with the to-be-marketed formulation using the highest proposed drug product strength. For additional information on designing a food effect study, refer to Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies.

3. It appears that a drug-drug interaction (DDI) study (Study NP17055) was conducted to assess the inhibition effect of palovarotene on the metabolism of midazolam. We recommend that drug interaction studies be conducted with palovarotene at a daily dose consistent with the highest proposed clinical dose (i.e., 20 mg based on your current proposed dose for Phase 3).

4. Address the influence of hepatic and renal impairment on the pharmacokinetics of palovarotene. For additional information, refer to (1) Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling; and (2) Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling.

5. Clarify if in vitro DDI studies have been conducted with palovarotene. For additional information, refer to Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. If in vitro DDI studies have been conducted, provide a summary of the findings from these studies and your plans for any further in vivo assessments.

Comments on the Study Protocol Synopsis (Study PVO-1A-301)

6. Pharmacokinetic samples should be collected after steady state is achieved. Instead of any time within the first 14 days of starting flare-up based treatment, collect pharmacokinetic samples between Day 4 and Day 28 of flare-up based treatment. In addition, to identify significant covariates such as age, body weight, and other factors and to confirm the validity of the weight-based dosing table, consider conducting population PK analysis in the Phase 3 study. To aid population PK analysis, characterize steady-state pharmacokinetic parameters in patients treated with the 5 mg maintenance daily dose or

weight-adjusted equivalent dose for both patients with flare-up and patients without flare-up.

7. Exclusion criterion #6 includes "concomitant mediations that are inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity." Clarify the rationale for this exclusion criterion, particularly the need to exclude weak inhibitors and inducers. If exclusion of CYP450 3A4 inhibitors and inducers is warranted, dietary supplements (e.g. St John's Wort) and some foods (e.g. grapefruit or grapefruit juice) that can induce or inhibit the activity of CYP3A4 enzyme should also be considered.

8. Record any concomitant medications.

9. The open label study design is a significant limitation for Patient-Reported Outcome (PRO) data interpretation. Patients' knowledge of treatment assignment may lead to systematic overestimation of the treatment effect, the magnitude of which is currently unknown. In settings where blinding is not feasible, or there is high likelihood of inadvertent unblinding due to toxicity, lack of blinding will need to be overcome by demonstrating a large and durable magnitude of effect in the setting of strict adherence to a carefully conducted clinical trial. PRO results can be further supported by findings from other endpoints and by sensitivity or subgroup analyses comparing the findings relative to other data collected in the trial. For instance, reduction in pain intensity measured by a PRO assessment could be further supported by reduced analgesic use.

10. Refer to Meeting Minutes dated March 21, 2017 regarding comments on the CAJIS and FOP-PFQ.

11. There are multiple versions of the PROMIS® Global Health instrument. Clarify which version will be used. Additionally, provide the exact copies of this instrument (and other questionnaires) in the final protocol.

12. In regards to the PROMIS® Global Health, in general, we have the following comments:
    - The PROMIS® Global Physical Health domain measures both symptoms and disease impacts. The general recommendation is to collect and analyze symptoms and impacts separately to the extent possible.
    - Some of the items in the PROMIS® Global Mental Health domain might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect. Refer to Additional Comment 9.

13. Additional considerations specific to pediatric populations should be taken into account when selecting an appropriate clinical outcome assessment, including: 1) selecting a well-defined and reliable instrument(s) that is developmentally appropriate for the entire age range included in the clinical trial population; and 2) using an instrument that is content and psychometrically valid for assessment in the patient population of interest.

Discussion at the Meeting:

1. Clementia confirmed that the formulation used in the Phase 2 studies and Phase 3 study will be the same as the to-be-marketed formulation and will provide drug product formulation in the summary table of clinical studies.
2. Clementia will perform a food effect study with the to-be-marketed formulation.
3. Clementia will repeat the CYP3A4 inhibition study with 20 mg palovarotene to steady state.
4. Based on the metabolism of palovarotene and the lack of liver impairment associated with FOP, Clementia does not plan to conduct a renal or hepatic impairment study. The FDA noted that patients with severe renal impairment may have altered drug metabolism. The FDA asked Clementia to submit data to support the rationale for not conducting these studies. Also, Clementia will check if the PK data in subjects with renal or hepatic impairment are available from the studies sponsored by Roche (b) (4)
5. In vitro drug-drug interaction (DDI) studies have been performed (see Slide 26). Clementia stated these data were included in the initial IND submission.
6. Clementia will modify the MOVE protocol to include recommended PK sampling during flare-up dosing at steady state. PK samples will be collected at steady state during the 5 mg chronic dosing. Clementia is unsure if they would have enough data for population PK analysis. The FDA explained the confirmatory data in Phase 3 will be important to confirm what we expect in the pediatric population.
7. Exclusion criterion #6 will be amended to "concomitant medication that are strong inhibitors or inducers of CYP450 3A4 activity."
8. Clementia will record concomitant medications.
9. Clementia agrees with the general comments on the interpretability of the PROs.
10. The PROMIS Global Health versions will be specified and appended to the protocol.

ADDITIONAL DISCUSSION:

- The FDA asked Clementia to provide the charter for computed tomography (CT) evaluation.
- The FDA stated Clementia should address the safety of blood volume for pediatric subjects with their protocol submission.

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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog)
(See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide)
(See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found
at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

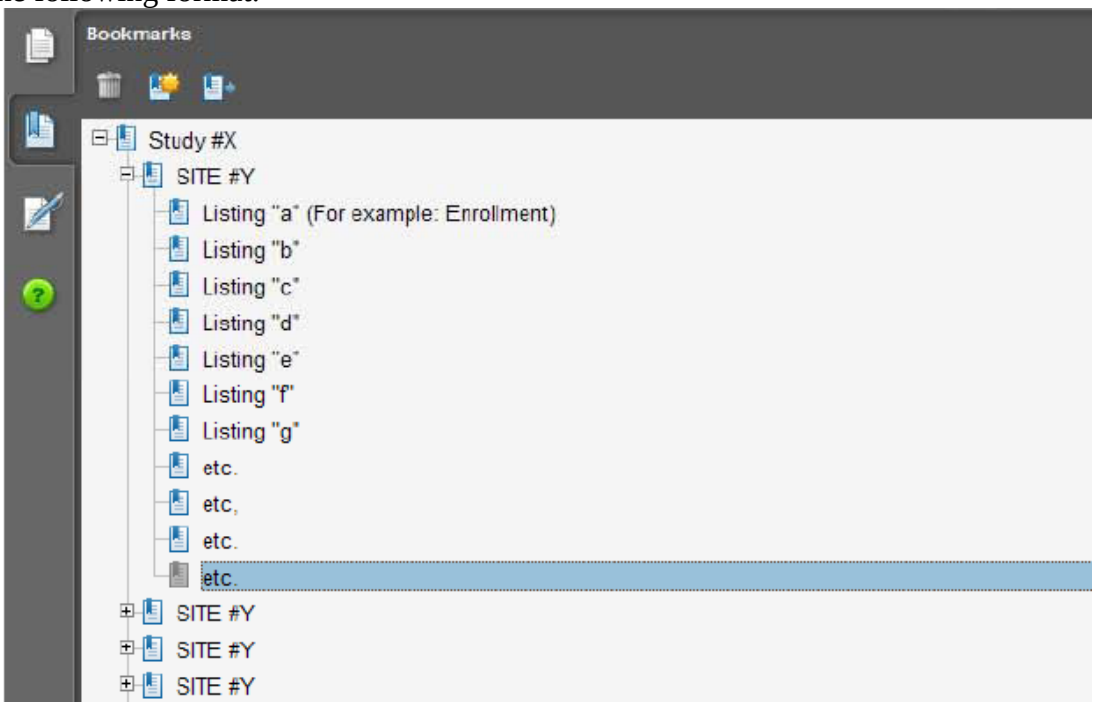
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Clementia will submit pediatric PK raw data, the SAP, and the Phase 3 protocol. The FDA will review and provide comments for the SAP and Phase 3 protocol.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	July 27, 2017

6.0 ATTACHMENTS AND HANDOUTS

End of Phase 2 Meeting Palovarotene for the Treatment of FOP

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

/s/

THERESA E KEHOE
07/20/2017