FAQs
CLINICAL PROGRAM

Clementia

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PROLOG

Clementia Pharmaceuticals is initiating the Phase 2 clinical program for palovarotene in patients with fibrodysplasia ossificans progressiva (FOP).

- **Study PVO-1A-201** is a Phase 2 double blind, placebo controlled clinical trial of palovarotene in FOP patients at the time of a flare-up. Patients who are at least fifteen years old, are experiencing a flare-up of the shoulders, arms, hips or legs, and for whom study medication can be started within seven days of the start of the flare-up will be randomized to receive either palovarotene or placebo for six weeks, with an additional six weeks follow-up. Twenty-four patients will be enrolled into this study: eighteen randomized to one of three doses of palovarotene and six to placebo. The purpose of this study is to determine whether palovarotene will have an effect on the formation of new bone during and following a flare-up, at what dose, and with what associated side effects. Clementia is also planning an open-label extension study to PVO-1A-201 for any patient who completes the twelve-week double-blind clinical trial.
- **Study PVO-1A-001** is a natural history study that will follow fifty FOP patients who are between two and sixty-five years old for up to three years. Patients will be evaluated annually for three years, with more frequent visits during a flare-up. The purpose of this study is to understand the relationship of new bone formation with clinical measures of physical function and quality of life and to monitor disease progression over time.

The following are questions and answers about specific aspects of Clementia's trials. These have been prepared to address certain questions the FOP community may have while ensuring compliance with the appropriate regulations regarding communication about an investigational drug. For more information about Clementia, click the home page button.

FREQUENTLY ASKED QUESTIONS

PALOVAROTENE

1. **What is palovarotene?**

   ANSWER: Palovarotene is a retinoic acid receptor gamma (RARγ) agonist and is in a class of compounds called systemic retinoids. These compounds have been shown to block bone formation in a variety of mouse models of FOP. Palovarotene is being investigated as a potential treatment for FOP.

2. **Has palovarotene been tested in animals?**

   ANSWER: Yes, palovarotene has been tested in both healthy animals and in animal models of FOP. The testing in healthy animals helped to determine what some of the potential side effects of palovarotene may be in humans. When tested in mouse models of FOP, palovarotene prevented new bone growth after injury in a dose related manner; that is, the higher the dose the more bone is prevented.

3. **What is the expected effect of palovarotene on humans with FOP?**

   ANSWER: Palovarotene prevented the formation of new bone in a variety of mouse models of FOP, but whether it will do the same in humans is not known. The Phase 2 clinical trial that Clementia is conducting is designed to evaluate the effect, if any, that palovarotene will have on new bone formation during and following a flare-up in patients with FOP, and at what dose. Additionally, this clinical trial will evaluate the side effects associated with palovarotene in patients with FOP.

4. **Have any people ever taken palovarotene? Were any of these patients afflicted with FOP?**

   ANSWER: Eight hundred and twenty-five people, including healthy volunteers and patients with emphysema, have taken palovarotene as of June 2014, but none of these were FOP patients.

PVO-1A-201, THE PHASE 2 CLINICAL TRIAL OF PALOVAROTENE IN PATIENTS WITH FOP

5. **What is the purpose of the Phase 2 palovarotene trial?**

   ANSWER: The purpose of this clinical trial is to investigate whether palovarotene has an effect on new bone formation during and following a flare-up in patients with FOP, at what dose and with what associated side effects.

6. **Who can participate in the Phase 2 Clinical Trial?**

ANSWER: This clinical trial is designed to observe the effects of palovarotene in FOP patients with the R206H mutation and will enroll 24 patients. Patients who are at least fifteen years old and are able to complete examination and enrollment within seven days of a flare-up that is located in the shoulders, arms, hips, or legs may be considered for enrollment in the Phase 2 clinical trial. Patients must be willing to receive treatment with prednisone per the FOP treatment guidelines; not have any of the clinical trial exclusion criteria; and must be able to attend all protocol scheduled visits during the 3-month trial. Further details and enrollment criteria of the clinical trial can be found on **www.clinicaltrials.gov**.

7. **Why is this Phase 2 clinical trial limited to twenty-four patients?**

ANSWER: Clinical trials are designed to provide the information that is needed to determine the safety and efficacy of the compound under investigation in the most efficient manner and with the lowest possible risk to patients. It was determined that 24 subjects would be sufficient to answer the question of whether palovarotene may prevent or decrease the amount of heterotopic ossification during and following a flare-up, and at what dose.

8. **Why can't children with FOP enroll in the Phase 2 Clinical trial?**

ANSWER: More information is required before children can be enrolled in a clinical trial with palovarotene. Clementia is conducting the necessary activities to obtain this information, which include additional animal and clinical studies.

9. **What is required of participants who are enrolled in the Phase 2 clinical trial?**

ANSWER: Patients will undergo a complete history plus a physical exam plus laboratory assessments to determine if they meet all the enrollment criteria for the clinical trial. Patients who meet the enrollment criteria and are enrolled in the clinical trial will then be randomly assigned to receive either palovarotene or placebo, which will be taken by the patient every morning after breakfast for 6 weeks. These patients will continue to be followed for an additional 6 weeks after study medication has stopped, so the total participation in the clinical trial is 12 weeks.

There will be a number of assessments that will be performed during the clinical trial to determine whether palovarotene will have an effect on new bone formation during a flare-up, and what the side effects are. These include x-ray, CT scan, and MRI of the flare-up site, patient rating of pain and swelling symptoms, and range of motion at the flare-up site. In addition, patients will complete questionnaires meant to assess physical limitations and other general health measures. Finally, side effects will be assessed. In general, these assessments will be performed at baseline (at the time of enrollment), at week 6 (at the end of treatment) and at week 12 (after the 6 week follow-up).

Further details of the clinical trial can be found on **www.clinicaltrials.gov**.

10. What does it mean to be randomly assigned to receive a placebo treatment in the Phase 2 clinical trial?

ANSWER: Patients who are enrolled in the Phase 2 clinical trial will be randomly assigned (a process similar to flipping a coin) to receive either palovarotene or placebo. In this clinical trial you will have a twenty-five percent (one in four) chance of receiving placebo and a seventy-five percent (three in four) chance of receiving palovarotene.

11. What is a placebo treatment and why is it being used in the Phase 2 clinical trial?

ANSWER: Placebo is a product with no therapeutic action that looks like the experimental compound but is not and does not contain palovarotene. Placebo treatments are usually required in clinical trials in order to determine whether an experimental compound provides any treatment benefit, and to determine the side effects. Using a placebo group in a clinical trial helps determine whether the effects seen are from the experimental compound, or are due to patients being carefully monitored as part of a clinical trial, or are by chance.

12. Will participants in the Phase 2 clinical trial be able to receive their usual care, like prednisone for a flare-up, other medications and/or devices (like oxygen, CPAP (continuous positive airway pressure), etc)?

ANSWER: Yes, although the clinical trial protocol does not allow some medications because of potential interactions with palovarotene, prednisone, oxygen, and CPAP are permissible. More details of the clinical trial, including acceptable medications, can be found on **www.clinicaltrials.gov**. Also, the clinical trial personnel will discuss this information with you.

13. What if a patient enrolled in the Phase 2 clinical trial experiences side effects to the treatment?

ANSWER: The most frequent side effects associated with palovarotene include effects on skin and mucous membranes (e.g. the inside of your nose and mouth) including dry skin, dry lips, itching, rash, redness of the skin, flaking and peeling skin, inflammation of the lips, dry mouth, and dry eyes.

There are other potential side effects associated with the class of medications palovarotene is a part of – called retinoids, and these will be described in the informed consent process when you are being considered for enrollment in the clinical trial. The patient will have the opportunity to discuss what these potential health risks are with the clinical trial personnel.

If a patient experiences a side effect during the clinical trial, he/she will be carefully evaluated by the clinical site physician and treated appropriately. Also, patients can choose to stop participating in the clinical trial at any time.

14. Where is the Phase 2 clinical trial being conducted?

ANSWER: The clinical trial is being conducted at three sites as listed below. There will be clinical trial personnel at each clinical site who are knowledgeable about FOP and well trained on the clinical study protocol. Site readiness details can be found on www.clinicaltrials.gov.

a. University of Pennsylvania – Clinical trial physicians: Dr. Robert Pignolo and Dr. Fred Kaplan
b. University of California, San Francisco – Clinical trial physician: Dr. Ed Hsiao
c. Hôpital Necker-Enfants Malades, Paris France – Clinical trial physician: Dr. Genevieve Baujat

15. Will a patient who does not live in the US or France be able to enroll in this clinical trial?

ANSWER: Yes, patients who live outside the US or France may be considered for enrollment into the trial, however, there are many practical challenges for these patients to be able to successfully participate in the study. These include rigorous travel requirements during a flare up: the patient must be able to arrive at the clinical site, undergo all screening activities, and start receiving the study medication within 7 days of the start of a flare-up; additionally, the patient must be able to come to the clinical site for all the required visits during the 12-week clinical trial, whether by commuting or relocating near the clinical site for the full 12-weeks. Also, because some of the endpoints involve patient reported outcome questionnaires, the patient must be fluent in English, French or Spanish. Final enrollment decisions will be made by the principal investigator.

16. Will Clementia provide funding for transportation and housing to participants in the Phase 2 clinical trial that live too far to drive to the clinic site?

ANSWER: Yes, all reasonable costs associated with participating in this trial will be covered, including travel and accommodations for the patient and a caregiver.

17. If this Phase 2 clinical trial is successful, will it lead to marketing approval?

ANSWER: This Phase 2 clinical trial is exploring whether palovarotene will have an effect on new bone formation during a flare-up in patients with FOP and at what dose. It will also assess the side effects of palovarotene in patients with FOP. Additional studies will be required before a regulatory agency such as the US Food and Drug

Administration and the EU European Medicines Agency will review the marketing application for palovarotene as a treatment for FOP.

18. What is the timeline for palovarotene marketing approval?

ANSWER: The timeline for marketing approval is not yet known.

19. What happens to patients after their participation in the Phase 2 clinical trial is complete?

- **ANSWER:** Clementia is planning an open-label extension study to PVO-1A-201 for any patient who completes the twelve week double-blind clinical trial.

Open-label means a patient enrolled in this extension clinical trial who experiences another flare-up would be treated with palovarotene whether or not that patient had received placebo or palovarotene in the first study. Details will be posted on www.clinicaltrials.gov when the clinical trial begins.

PVO-1A-001 THE NATURAL HISTORY STUDY

20. What is a natural history study?

ANSWER: A natural history study is a specific type of clinical trial that tracks the progression of a disease over time in patients who are receiving their currently available treatments only. The information collected in a natural history study can be used to understand how a disease typically progresses and how an investigational treatment might affect the course of the disease.

21. Why is Clementia conducting the Natural History Study in patients with FOP?

ANSWER: The Natural History Study will document the patient experience with FOP in a scientifically rigorous manner. The information gathered will be very useful for designing palovarotene's clinical plan and understanding its place in the treatment of FOP. The natural history study will be conducted in parallel with the Phase 2 clinical trial.

22. What does Clementia's Natural History Study entail?

ANSWER: Annual visits will be performed over three years, during which the patient will complete questionnaires about their FOP and how it impacts their life, undergo an assessment of range of motion across the major body regions and joints and blood tests will be obtained, including some potential biomarkers of disease. In addition, the amount of HO as measured by whole body CT scan (excluding the head) and DEXA scan – like having your bone density measured, will also be performed.

Should you experience a flare-up during the 3-year follow-up, more careful assessments at the time of the flare-up will also be performed, including x-rays and CT scan at the flare-up site.

Specific details about the Natural History Study are provided on www.clinicaltrials.gov.

23. Who can participate in the Natural History Study?

ANSWER: Patients with a diagnosis of classical FOP due to the R206H mutation between the ages of 2 and 65 years are eligible to participate. The gene mutation will be determined at study entry, and patients with mutations other than R206H will not be able to participate. Specific study details are provided on www.clinicaltrials.gov, which includes a 1-800-XXX-XXXX to obtain additional information.

24. Will a patient who is enrolled in the Natural History Study be able to enroll in the Phase 2 clinical trial for palovarotene?

ANSWER: Yes, a patient who is enrolled in the natural history study and experiences a flare-up will be able to enroll in the Phase 2 clinical trial if that patient meets the Phase 2 clinical trial enrollment criteria and the Phase 2 clinical trial is still enrolling patients. The patient cannot be enrolled in both trials, so the patient would be discontinued from the Natural History Study once enrolled the Phase 2 trial.

25. How is this Natural History Study different from the flare-up survey and the registry the IFOPA is planning?

ANSWER: The flare-up survey was a one-time, cross-sectional patient report of disease and flare-up symptoms in about 500 patients, conducted by the Center for Research in FOP & Related Disorders at The University of Pennsylvania.

The Natural History Study is a prospective longitudinal study that will collect specific standardized information over a 3-year period in about 50 patients from about 10 doctors.

The IFOPA registry will collect information directly from patients, and eventually also collect clinical assessments and test results from doctors. The registry will be available to all FOP patients and doctors worldwide and is expected to last for 10 or 20 years. The choice of information collected in the IFOPA registry will be determined by the flare-up survey, by Clementia's natural history study, and by experts who will help advise the registry.

All three approaches – the flare-up survey, the NHS and the IFOPA Registry will provide complementary information that will improve the understanding of FOP, and will help to inform the design of trials for investigational products for FOP.