

# Phase 2 Open Label Extension Trial FAQs – Part B

- What is the status of the Clementia clinical program for FOP?..... 2
- What is Part B?..... 2
- What is palovarotene?..... 2
- Has palovarotene been tested in animals?..... 2
- What are the new dosing regimens? ..... 3
- What is an eligible flare-up? ..... 3
- Does this modification suggest anything about whether palovarotene works or not? ..... 3
- What are the potential side effects of the higher doses of palovarotene that are being evaluated in Part B?..... 4
- Will participants in Part B of the Phase 2 Open-Label Extension clinical trial be able to receive their usual care such as prednisone for a flare-up, other medications, and/or devices like oxygen or CPAP (continuous positive airway pressure)? ..... 4
- Who is eligible to participate in Part B of the Open Label Extension Study? ..... 4
- What does participation in the study involve? ..... 4
- Where is the trial being conducted?..... 6
- Does Clementia cover the costs to participate in the trial? ..... 6
- What happens when Part B is complete?..... 6
- What happened to the “In Home” study (PVO-1A-203)?..... 6
- When is the Phase 3 trial expected to begin? ..... 6
- What is the timeline to marketing approval? ..... 6
- Does participation in Part B prohibit me from participating in any other trial including the Phase 3 trial? ..... 7
- Does participation in the Natural History Study (PVO-1A-101) prohibit me from participating in Part B? ..... 7
- Is palovarotene available to people who are not enrolled in Part B? ..... 7

## What is the status of the Clementia clinical program for FOP?

The Clementia clinical program is collecting and analyzing data on the safety and efficacy of palovarotene as a potential treatment for FOP. These data will be included in a marketing application, which will be submitted to regulatory authorities, such as the US Food and Drug Administration or the EU European Medicines Agency, for consideration and potential approval of palovarotene as a treatment for FOP. The clinical studies are listed in the table below.

Phase 2 Trial (PVO-1A-201)	Phase 2 Open-label Extension Trial (PVO-1A-202)		Natural History Study (PVO-1A-001)
	Part A	Part B	
Complete	Complete	Enrolling	Enrolling
Phase II, randomized, double-blind, placebo-controlled study evaluating the effect of two different doses of palovarotene on new bone formation during and after a flare-up in individuals with FOP.	Open-label, Phase II extension study evaluating the long-term safety and efficacy of palovarotene on new bone formation during and after a flare-up.	Open-label, Phase II extension study evaluating dose exploration in individuals with FOP.	A non-interventional, longitudinal natural history study in people with FOP designed to understand disease progression and impact over time.

## What is Part B?

Part B is not a new trial, but rather a modification of the Phase 2 Open-label Extension Trial (PVO-1A-202) that includes new palovarotene dosing regimens. The purpose of Part B is to evaluate the safety and efficacy of a chronic dosing regimen as well as an acute flare-up dosing regimen that is higher in dose and longer in duration than what was previously studied in the Phase 2 trials. The expanded dose exploration is key to this stage in drug development and will greatly inform the design of any subsequent trials.

## What is palovarotene?

Palovarotene is an oral compound and a retinoic acid receptor gamma (RAR $\gamma$ ) agonist. Palovarotene is part of a class of compounds called systemic retinoids. Palovarotene has been shown to block heterotopic ossification (HO) in mouse models of FOP. HO is normal bone that has formed in an abnormal place. Palovarotene is being investigated as a potential treatment for FOP, a disease characterized by HO, in Clementia clinical trials.

## Has palovarotene been tested in animals?

Palovarotene has been tested in both healthy animals and animal models of FOP. The testing in healthy animals helped to determine potential side effects of palovarotene in humans. When tested in mouse models of FOP, chronically administered palovarotene prevented spontaneous heterotopic ossification. Also, palovarotene prevented HO in a trauma induced model in a dose-dependent manner, meaning that higher doses resulted in greater degrees of HO inhibition with highest doses resulting in complete HO inhibition.

## What are the new dosing regimens?

In Part B, participants are separated into two groups, an adult cohort and a pediatric cohort, based on skeletal maturity. Chronic dosing, which may help to ensure that drug is present before recognition of flare-up symptoms and is frequently used in other diseases with flare-up or acute presentations, will first be evaluated in the adult cohort that includes adults and teenagers who are nearly grown (>90% skeletal maturity). The safety and efficacy of chronic dosing needs to be evaluated in the adult cohort before it can be used in actively growing children in the pediatric cohort. During eligible flare-ups, all participants will receive acute dosing, which is higher in dose and longer in duration than what was previously studied. There is no placebo in Part B so all participants receive palovarotene. The exact dosing and treatment duration is displayed in the table below.

Dosing Regimen	Palovarotene Dosing		Treatment Duration
	Adult Cohort	Pediatric Cohort	
<b>Chronic</b>	5 mg	None*	Daily
<b>Acute Flare-up Dose</b>	20 mg	Weight adjusted equivalent	Up to 28 days (4 weeks)
	10mg	Weight adjusted equivalent	At least 56 days (8 weeks)
	The first dose will be taken upon flare-up confirmation by the principal investigator  Dose reductions will occur if the dose is not tolerated		The total treatment duration is 84 days (12 weeks)  Treatment may be extended if the flare-up is ongoing at Day 84 and continue until the flare-up resolves

\*The safety and efficacy of chronic dosing needs to be evaluated in the adult cohort before it can be used in actively growing children in the pediatric cohort.

Further details can be found on [www.clinicaltrials.gov/ct2/show/NCT02279095](http://www.clinicaltrials.gov/ct2/show/NCT02279095) and [www.orpha.net](http://www.orpha.net).

## What is an eligible flare-up?

A flare-up is characterized by at least two of the following symptoms: pain, swelling, decreased range of motion, stiffness, warmth, or redness. An eligible flare-up is one that occurs in the arms, legs, hips, chest, abdomen, neck, or lower back. Study participants should contact the clinical trial site team immediately upon suspicion of a flare-up in any body region.

## Does this modification suggest anything about whether palovarotene works or not?

No. The Phase 2 trial (PVO-1A-201) in which enrollment is now complete was designed as an exploratory dose-ranging study and examined the safety and efficacy of two different doses of palovarotene in participants with an acute flare-up. The Open-Label Extension Trial (PVO-1A-202) was designed to evaluate longer-term safety and efficacy of palovarotene in individuals who participated in the Phase 2 double-blind trial. Emerging data from the Open-Label Extension Trial has suggested that the risk of developing heterotopic ossification may not be the same for all flare-ups. This learning and others have allowed us to move forward and explore new dosing regimens.

## What are the potential side effects of the higher doses of palovarotene that are being evaluated in Part B?

The most frequent side effects associated with palovarotene affect the skin and mucous membranes inside the nose/mouth and include dry skin, lips, mouth or eyes; inflammation of the lips; itching; rash or skin redness; and flaky or peeling skin. These side effects, which are treated with moisturizers and antihistamines, may occur more frequently or be more bothersome with the higher doses of palovarotene. Children will also be monitored for possible side effects related to growing bones.

The principal investigator has the option of reducing the dose if side effect symptoms are not tolerated or may recommend certain treatments to try to prevent side effects. Make sure to notify the principal investigator of any side effects while taking palovarotene.

## Will participants in Part B of the Phase 2 Open-Label Extension clinical trial be able to receive their usual care such as prednisone for a flare-up, other medications, and/or devices like oxygen or CPAP (continuous positive airway pressure)?

The clinical trial protocol does not allow some medications because of potential interactions with palovarotene; but, it is permissible to use prednisone, oxygen, and CPAP. The clinical trial site personnel will discuss acceptable and nonacceptable medications in more detail.

Further details on acceptable medications can be found on [www.clinicaltrials.gov/ct2/show/NCT02279095](http://www.clinicaltrials.gov/ct2/show/NCT02279095) and [www.orpha.net](http://www.orpha.net).

## Who is eligible to participate in Part B of the Open Label Extension Study?

All 40 individuals who have completed the Phase 2 trial (PVO-1A-201) may enroll and up to 20 new adults or teenagers who are nearly grown may be eligible for enrollment into the adult cohort. In order to participate in the Open-label Extension trial, new participants will need to meet all enrollment criteria.

Eligible new participants must:

- ✓ Reside in the US, Canada, UK, or France due to regulatory requirements
- ✓ Have had at least two self-reported flare-ups in the last two years but cannot have had flare-up symptoms in the last four weeks at time of enrollment
- ✓ Have achieved 90% skeletal maturity (if under age 18), which means that the bones are almost done growing as measured at enrollment screening
- ✓ Have some movement limitations in joints but not complete locking of most joints as determined by the site principal investigator using a standardized assessment
- ✓ Have the most common mutation, R206H, associated with FOP as confirmed by genetic testing performed at enrollment screening
- ✓ Be willing to consider treatment with prednisone according to the FOP treatment guidelines
- ✓ Be able to attend all scheduled site visits during the trial
- ✓ Meet all other enrollment criteria

Further details and additional enrollment criteria can be found on [www.clinicaltrials.gov/ct2/show/NCT02279095](http://www.clinicaltrials.gov/ct2/show/NCT02279095) and [www.orpha.net](http://www.orpha.net).

## What does participation in the study involve?

Study participation involves travel to a clinical trial site, remote visits, and telephone calls in order to complete all of the necessary assessments. Site visits require travel to a clinical trial site, while remote visits are performed at the participant's home by qualified study personnel or at a local medical facility, when possible.

The assessments and their schedules differ depending on the participant's dosing regimen and cohort as displayed below. Anyone with questions about the assessments should contact the clinical trial site team for discussion of risks, benefits, or limitations. Further details can be found on [www.clinicaltrials.gov/ct2/show/NCT02279095](http://www.clinicaltrials.gov/ct2/show/NCT02279095) and [www.orpha.net](http://www.orpha.net).

Assessments	Assessment Schedule for Chronic Dosing Regimen (Adult Cohort Only)				
		Screening Site Visit	Site Visit or Remote Visit (where possible) Monthly	Site Visit or Remote Visit (where possible) Every three months (except when overlaps with annual site visit)	Site Visit Study Months 12 & 24
	<b>Imaging</b>	– Low-dose whole body CT scan (excluding head) – X-rays (hand/wrist & knee)**			– Low-dose whole body CT scan (excluding head)
	<b>Physical examination</b>	✓			✓
	<b>Blood/Urine testing</b>	✓	✓*	✓	✓
	<b>Questionnaires/ Self-assessments</b>	✓			✓
	Assessment Schedule with No Dosing (Pediatric Cohort only)				
		Screening & Monthly Telephone Contacts Months 6, 18 and 24		Site Visit Month 12	
	<b>Imaging</b>			–X-rays (hand/wrist & knee)** –Low-dose CT scan***	
	<b>Physical examination</b>			✓	
<b>Blood/Urine testing</b>			✓		
Assessment Schedule for Acute Dosing Regimen for Eligible Flare-ups (Adult and Pediatric Cohorts)					
	Site Visit Flare-up Screening/ Baseline	Site Visits or Remote Visits (where possible) Every two weeks until end of treatment	Site Visit Flare-up Day 84/End of Treatment		
<b>Imaging</b>	– X-rays (hand/wrist & knee)** – Low-dose CT scan (flare-up site)*** – MRI (flare-up site)****		– X-rays (hand/wrist & knee)** – Low-dose CT scan (flare-up site)*** – MRI (flare-up site)****		
<b>Physical examination</b>	✓		✓		
<b>Blood/Urine testing</b>	✓	✓	✓		
<b>Questionnaires/ Self-assessments</b>	✓	✓	✓		

\*Only urine-based pregnancy testing for women who are able to become pregnant.

\*\*Only for participants <18 years old or in pediatric cohort in order to measure skeletal maturity

\*\*\*X-rays will be performed if the participant is unable to undergo CT scan.

\*\*\*\*Ultrasound may be performed if the participant is unable to undergo MRI.

### Where is the trial being conducted?

ANSWER: Part B will be conducted at four sites as listed below. At each site, there are clinical trial personnel who are knowledgeable about FOP and well trained on the study protocol. Each site must receive approval by its national regulatory authority and by its hospital ethics committee prior to enrolling individuals into Part B. Any person with FOP who resides in the US, Canada, UK, or France and is interested in participating should contact one of the clinical trial sites directly.

Site	Principal Investigator	Phone Number
University of Pennsylvania, Philadelphia US	Robert J Pignolo, MD, PhD	+ 1 215-294-9112
University of California, San Francisco US	Edward Hsiao, MD, PhD	+ 1 415-353-9087
Hôpital Necker-Enfants Malades, Paris France	Genevieve Baujat, MD	+ 33 7-85-98-05-46
Royal National Orthopaedic Hospital, London England	Richard Keen, BSc, PhD	+ 44 208-909-5425

More information can be found at: [www.clementiapharma.com/clinical-trials/participating-clinical-trial-sites/](http://www.clementiapharma.com/clinical-trials/participating-clinical-trial-sites/), [www.clinicaltrials.gov/ct2/show/NCT02279095](http://www.clinicaltrials.gov/ct2/show/NCT02279095) and [www.orpha.net](http://www.orpha.net).

### Does Clementia cover the costs to participate in the trial?

ANSWER: All reasonable costs associated with participating in the trial will be covered including travel, meals, and accommodations for the study participant and up to two caregivers. Travel and accommodations are booked by an agency that specializes in travel planning for individuals with restricted mobility.

### What happens when Part B is complete?

ANSWER: The Part B results plus those of Clementia's other Phase 2 trials and Natural History Study will be instrumental in designing future clinical trials in FOP, and Part B participants who meet other eligibility criteria will be offered participation in a separate long-term, open-label extension trial.

### What happened to the "In Home" study (PVO-1A-203)?

ANSWER: When Part B begins, the In Home study will be placed on hold in order to safely evaluate the new dosing regimens. It is necessary to obtain data on these new dosing regimens before re-initiating the In Home study.

### When is the Phase 3 trial expected to begin?

ANSWER: The timing of the initiation of a Phase 3 trial is not yet known. Data from Clementia's Phase 2 trials and ongoing Natural History Study will be essential in informing the design of the Phase 3 trial and when it can be initiated.

### What is the timeline to marketing approval?

ANSWER: The timeline to marketing approval is not known. Once Part B is complete, the data will be analyzed to assess palovarotene's effectiveness and safety. Additional studies, such as a Phase 3 trial, will likely be required before a regulatory agency such as the US Food and Drug Administration or the EU European Medicines Agency will review the marketing application for palovarotene as a treatment for FOP.

Does participation in Part B prohibit me from participating in any other trial including the Phase 3 trial?

ANSWER: It is not possible to know the enrollment criteria of future studies. However, participants can choose to leave Part B at any time.

Does participation in the Natural History Study (PVO-1A-101) prohibit me from participating in Part B?

ANSWER: Participants in the Natural History Study may transfer into Part B if they meet all eligibility criteria but cannot participate in both studies at the same time.

Is palovarotene available to people who are not enrolled in Part B?

ANSWER: As an investigational therapy, palovarotene is currently only available in an approved clinical trial. The main purpose of the Phase 2 program is to determine whether palovarotene can prevent new bone formation at the time of a flare-up, at what dose, and with what side effects. Data from the Phase 2 trial (PVO-1A-201) and the Phase 2 Open-label Extension trial (PVO-1A-202, Parts A and B) will provide preliminary answers to these questions. Clementia is working rapidly and diligently to obtain and analyze the data needed to determine safety and efficacy and to design the next steps in the palovarotene clinical program.

Individuals not in the Phase 2 trial can choose to participate in the Natural History Study, which is advancing our understanding of disease and is a key component of our clinical program. This trial is already providing critical data that we think will help improve our future strategies for managing FOP.