Next Step in Clementia's Clinical Program for Fibrodysplasia Ossificans Progressiva (FOP)

Thank you for considering participation in Part B of the Phase 2 Open-label Extension clinical trial. This trial is investigating palovarotene as a potential treatment for FOP and has been modified to include new palovarotene dosing regimens. The expanded dose exploration is key to this stage in drug development and will greatly inform the design of any subsequent trials.

The below frequently asked questions (FAQs) will help you to understand Part B of the Open-label Extension trial, and what you need to do to enroll. The principal investigator and clinical site team will have a more detailed discussion with you about the study requirements and the potential risks and benefits of your participation in Part B.

FAQs

What is Part B?

Part B is not a new trial but rather a modification of the ongoing Open-label Extension trial (PVO-1A-202) that is evaluating the safety and efficacy of palovarotene as a potential treatment for FOP. Palovarotene is an oral compound and a retinoic acid receptor gamma (RARγ) agonist that is part of a class of compounds called systemic retinoids. Palovarotene has been shown to block heterotopic ossification (HO) in mouse models of FOP.

Who is eligible to participate in Part B?

Clementia is enrolling up to 20 new adults as well as teenagers who are nearly grown into Part B. In order to participate in the Open-label Extension trial, you 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 their bones are almost done growing as measured by height assessments and by X-rays of the hands/wrists and knees 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

What are the dosing regimens being explored?

Part B is designed to explore chronic dosing between flare-ups and acute dosing during an eligible flare-up that is higher in dose and longer in duration than what was studied in the Phase 2 trial. Chronic dosing may help to ensure drug exposure before recognition of flare-up symptoms. There is no placebo in Part B so all participants receive palovarotene. The exact dosing and treatment duration is displayed in the table below.

		Palovarotene Dosing	Treatment Duration
Dosing Regimen	**Chronic**	5 mg	Daily
	Acute Flare-up Dose*	20 mg	Up to 28 days (4 weeks)
		10mg	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

*A flare-up involves at least two of the following symptoms: warmth, redness, soft tissue swelling, pain, or limited/loss of movement (decreased range of motion). An eligible flare-up is one that occurs in the arms, shoulders, legs, hips, chest, abdomen, neck, or lower back.

What are the potential side effects of palovarotene?

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 higher doses of palovarotene.

The principal investigator has the option of reducing the dose if side effect symptoms become bothersome or may recommend certain treatments to try to prevent side effects. Make sure you notify your principal investigator of any side effects while taking palovarotene.

What does participation in Part B involve?

Part B involves travel to the clinical trial site, remote visits, and telephone calls in order to complete all of the necessary assessments. The assessments and their schedules differ depending on the participant's dosing regimen and cohort as displayed below.

Dosing Regimen		**Assessments**	**Screening Site Visit**	**Remote Visit** Monthly	**Remote Visit** Every three months (except when overlaps with annual site visit)	**Site Visit** Study Months 12 & 24
	Chronic	**Imaging***	✓			✓
		Physical examination	✓			✓
		Blood/Urine testing	✓	✓**	✓	✓
		Questionnaires/Self-assessments	✓			✓
		Assessments	**Site Visit** Flare-up Screening/ Baseline	**Remote Visits** Every two weeks until end of treatment	**Site Visit** Flare-up Day 84/End of Treatment	
	Acute Flare-up Dose*	**Imaging***	✓		✓	
		Physical examination	✓		✓	
		Blood/Urine testing	✓	✓	✓	
		Questionnaires/ Self-assessments	✓	✓	✓	

*Imaging may include low dose CT scan, MRI, ultrasound, or X-ray.
**Only urine-based pregnancy testing for women who are able to become pregnant.

What happens when Part B is complete?

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.

Does Clementia cover the costs to participate?

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.

How do I enroll?

The principal investigator and clinical trial site team can explain the informed consent process and may provide additional information about the trial requirements.

Site	Principal Investigator	Phone Number
University of Pennsylvania, Philadelphia USA	Robert J Pignolo, MD, PhD	+ 1 215-294-9112
University of California, San Francisco USA	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

How do I find out more information?

Further details can be found at www.clinicaltrials.gov, www.orpha.net, and www.clementiapharma.com.