clementia

MO-Ped Trial FAQs

1. Is MO, HMO, HME, and MHE all the same disease?

Yes. Multiple Osteochondromas (MO) has many names, including Hereditary Multiple Osteochondromas (HMO), Multiple Hereditary (or hereditary multiple) Exostoses (MHE or HME), or familial exostoses. The different names come from the use of "osteochondromas" or "exostoses" to describe the bone growths that occur with MO and the hereditary nature of the disease. The term osteochondromas is preferred since it is a more accurate medical description of the formation of cartilage growths that later ossify (or turn to bone), and we will use the term MO to refer to the condition throughout this document.

2. What is the MO-Ped Trial?

The MO-Ped Trial (**M**ultiple **O**steochondromas in **Ped**iatrics) is a global Phase 2 clinical study designed to evaluate the efficacy and safety of two dosages of palovarotene versus placebo (i.e. sugar pill), in pediatric subjects. Each subject will receive 2 years of study drug, and the study ends when all phases of the study including the last visit or any scheduled follow-up procedures have been completed. All subjects who complete the MO-Ped Trial may be eligible to enroll in a follow-up study. In this follow-up study, all enrolled subjects will receive palovarotene. If the therapeutic efficacy of palovarotene is unexpectedly large, the trial may end early at a 1-year interim analysis.

3. Who can participate in the MO-Ped Trial?

The MO-Ped Trial will enroll both male and female pediatric subjects from 2 to 14 years of age to assess palovarotene's effect on osteochondroma formation and other related events that impact a subject's physical function and quality of life. We are testing if palovarotene is effective in preventing new osteochondroma formation and growth, which are thought to occur only while the growth plate is active. The 14-year-old age and bone age limit would permit at least 2 years of observation while the growth plate is active. All individuals must weigh at least 10 kg, and must have a genetic diagnosis of Multiple Osteochondromas (MO) with exostosin 1 or 2 (Ext1 or Ext2) mutations confirmed by a central laboratory. Both individuals with a spontaneous mutation or an inherited mutation are eligible for this trial.

Please note that an individual interested in participating in the MO-Ped Trial does not have to be genetically tested before the trial starts, as the gene test will take place during the screening visit.

Subjects must also have symptomatic MO, which is defined as any of the following:

- A new or enlarged osteochondroma that occurred in the preceding 12 months.
- A painful osteochondroma, skeletal deformity, or a limitation in joint movement.
- A prior surgery for an MO-related complication.

Additional inclusion and exclusion criteria are available at www.clinicaltrials.gov. Subjects must also comply with study visits and assessments to qualify and these will be explained to you by the study physician.

4. What is the purpose of MO-Ped Trial and what are the clinical endpoints?

The purpose of the MO-Ped Trial is to evaluate the efficacy and safety of two palovarotene dosage regimens on MO patients and to determine whether treatment with palovarotene over 24 months can reduce new osteochondroma formation, the volume of osteochondromas, new or worsening of limb deformities, or MO-related surgeries.

5. What is palovarotene?

Palovarotene is an investigational medicinal product belonging to a group of compounds called retinoids. It is specifically classified as a selective retinoic acid receptor gamma agonist (RARγ). Clementia is developing palovarotene as an orally administered treatment for patients with Multiple Osteochondromas (MO) and for another rare bone disease known as fibrodysplasia ossificans progressiva (FOP).

Palovarotene has been studied in over 800 humans, including healthy volunteers, people with COPD, and individuals with FOP. Safety information has been gathered from pediatric patients with FOP. Side effects involve the skin and mucous membranes (e.g., lining inside of your nose and mouth) and not other organs in the body. Specifically, side effects of dry skin, dry lips, itching, rash, redness, mouth sores, and hair loss are seen. In general, the number, severity, and duration of these mucocutaneous and dermatologic side effects increased as the palovarotene dose increased. Most of these were mild or moderate in severity and generally resolved or improved after treatment with skin lubricants, lip balms, antihistamines, or by decreasing the dose of palovarotene if necessary.

Effect on bones and skeletal growth are especially important for pediatric subjects. In juvenile animals administered palovarotene, minor shortening of the limb bones has been observed particularly in younger animals and at high doses. At doses to be used in the MO-Ped trial, any potential abnormalities observed are predicted to be mild and at least partially reversible after the treatment is stopped. In the FOP studies, growth plates and linear heights were examined in children who are still growing and received episodic high dose treatment during flares. Appropriate increases in bone age, linear and knee height were observed in most subjects. No premature closure of the growth plate was noted in any subject. In the MO-Ped trial, safety monitoring for bone effects and growth will occur to identify any potential adverse growth effects.

6. How will the treatment be administered?

Palovarotene is a once a day pill. Specifically, powder-filled gelatin capsules are preferably taken following the first meal of the day. Absorption of the medicine is better with a full meal. For younger children who may have difficulties swallowing intact capsules, parents may sprinkle the contents of the capsule onto a teaspoon of food (such as pudding, yogurt), so that the entire dose can be taken.

7. How is the dosing determined for palovarotene for children?

The dosages of palovarotene to be tested in MO-Ped Trial are chosen to maximize the inhibition of osteochondroma growth and to minimize risk of adverse effects. These doses are based on the Multiple Osteochondromas (MO) animal data on efficacy and safety, preliminary pharmacokinetic data from subjects with Fibrodysplasia Ossificans Progressive

(FOP), as well as clinical safety data from subjects with Chronic Obstructive Pulmonary Disease (COPD) and FOP. The doses to be tested are 2.5 and 5 mg once daily and are adjusted by weight so that the amount in the blood is in the range that is targeted for the desired drug effects and to minimize potential adverse effects.

8. **Why does Clementia believe this drug may be effective for the treatment of MO?**

Research in a mouse model of MO (Multiple Osteochondromas) shows that palovarotene potently inhibits the formation of new osteochondromas by decreasing signaling in the bone morphogenetic protein pathway (BMP pathway) in bone precursor cells. These animals develop osteochondromas as they age, developing hundreds of osteochondromas on their ribs and limb bones by 6 weeks of age. Treatment with palovarotene from a young age at doses equivalent to test doses in the MO-Ped trial inhibited osteochondroma formation by 30-80% compared with mice not receiving palovarotene treatment.

Additionally, Clementia has data from FOP (Fibrodysplasia Ossificans Progressiva) patients treated with palovarotene that demonstrates substantial decreases in the amount of abnormal bone that is seen in these FOP patients (up to 95% reduction in mean bone volume following flare-up treatment). MO and FOP share the same disease process of excess bone morphogenetic protein signaling within cells resulting in chondrogenesis (cartilage formation) and further ossification (bone formation).

Together, these data showing efficacy in MO animals and FOP patients and the safety data from more than 800 human subjects who have been treated with palovarotene support the idea that palovarotene may be effective in patients with MO in the MO-Ped Trial.

As osteochondroma growth only occurs while the growth plate is active, palovarotene is likely only effective in preventing new OC formation and subsequent joint deformity, loss of function, need for surgery in pediatric MO patients. The objective of the MO-Ped Trial is to assess palovarotene's effect on osteochondroma formation, and these other related events that impact a subject's physical function and quality of life.

9. **Do you expect any difference in palovarotene efficacy between males and females?**

No. While multiple studies have shown that male patients with MO tend to have more severe disease, it is not known why. The study is designed in a way for us to determine if there is a difference in efficacy and safety between males and females.

10. **Are there potential risks in administering palovarotene to children that are still growing?**

Experience with palovarotene from clinical trials in another rare bone disease, fibrodysplasia ossificans progressiva (FOP), has not shown treatment-related side effects on bone growth plates or height with weight-adjusted doses of palovarotene and with higher doses (up to 20 mg) administered during episodes of soft tissue swelling (flare-ups). The MO-Ped Trial will include strict safety monitoring for any potential skeletal effects associated with bone growth plates and linear growth.

The reason for caution is that the biological process by which palovarotene inhibits osteochondroma formation may also affect normal bone growth in children. Results from animal research showed that impaired growth may occur if palovarotene treatment is started at a very young age. This effect is alleviated with lower doses or by beginning treatment at older ages.

The selection of ages for subjects in the MO-Ped Trial (2 to 14 years) takes into consideration the findings in animal models and provides an optimal age range balancing the potential benefit of palovarotene treatment while minimizing potential risks. This targeted population, coupled with the doses selected to be administered and the careful monitoring for potential adverse growth effects should help minimize any potential risks.

All subjects will have x-rays of the hand/wrist area and knee along with linear and knee height measurements every 6 months to monitor bone growth plate and growth. The growth of long bones of the legs (tibia and femur) will also be monitored. The bone thickness of the lumbar spine, hip and radius will be assessed by dual –X-ray absorptiometry (DXA) every 6 months. Dose modification or discontinuation will be considered should adverse effects be identified.

11. Why is a placebo needed in the MO-Ped Trial?

Our goal is to answer key questions about the true treatment effect of palovarotene for Multiple Osteochondromas (MO). It is by comparing the efficacy and safety to a placebo group that we can carefully assess the efficacy and safety of the investigational drug. This is especially true for diseases where there have not been previous clinical trials to determine the natural course of disease progression.

Therefore, the MO-Ped Trial will be a “placebo- controlled, treatment- blind study”.

12. What happens if I’m in the placebo group?

The MO-Ped Trial has three treatment groups. Two groups will receive one of two daily dosages of palovarotene and the third group will receive placebo. However, because treatment is “blinded,” no one knows who is assigned to which group, including the subject, caregivers, study physician and study site personnel and Clementia. All other procedures and assessments remain the same for all subjects. At study enrollment, subjects will go through a randomization process (like flipping a coin) that determines which treatment they will receive. This process ensures an equal number of subjects are assigned across the three groups. The chance is one out of three that a subject would be assigned to the placebo group, and two out of three for assignment to a palovarotene group. When the subject completes participation in the MO-Ped Trial, the subject may be eligible for an open label extension study. All subjects from the MO-Ped Trial including those who had received placebo will receive palovarotene in the extension trial.

13. Will subjects in the MO-Ped Trial be able to receive their usual care?

Yes. Subjects will receive their usual standard of care treatments for Multiple Osteochondroma (MO). For example, the study physician may administer pain medication, or undergo surgery to remove a painful osteochondroma, or to correct a deformity or a functional limitation in the movement of a joint. However, some medicines are not

permitted during the MO-Ped trial because they may interfere with palovarotene. These are not frequently used medicines and usually, a substitute can be used. Clinical study personnel will discuss this information with you during the study screening process.

14. Are MO-related surgeries allowed during participation in the MO-Ped Trial?

Yes, surgeries for the treatment of Multiple Osteochondromas (MO) are part of the standard of care and therefore are allowed during the MO-Ped Trial

15. What if a subject enrolled in the MO-Ped Trial experiences side effects due to the treatment?

Side effects are monitored throughout the MO-Ped Trial. Any subject who experiences a side effect during the MO-Ped Trial will be evaluated by the study physician and study site staff and treated appropriately. As a part of the management of side effects, the study physician may instruct a subject to decrease the frequency of dosing or stop treatment (either temporarily or permanently). All subjects have the option to stop their participation in the MO-Ped Trial at any time without affecting any treatments they would normally receive.

Known potential side effects will be described in the informed consent form. This form is a detailed document that the study physician and/or study staff will discuss thoroughly with potential subjects during the enrollment evaluation. The evaluation process gives potential subjects an opportunity to ask any questions regarding the MO-Ped Trial, including questions about the potential health risks and safety monitoring.

16. Why do you do MRI and what does that mean for my child?

Magnetic resonance imaging (MRI) is the best way to image the structure and size of osteochondromas and to visualize the relationship of osteochondromas to the normal skeleton. Using MRI, we can count the number of osteochondromas in the body and measure the total volume of these osteochondromas. This is one of the measures to assess palovarotene's potential effects on osteochondroma growth. Whole body MRIs will be performed at the first study visit, every 12 months during the study, and at early conclusion for subjects who discontinue the study prior to its completion.

MRI uses a large magnet to visualize the body parts; so, there is no radiation, it is not painful but it does take a long time and makes loud noises. Your child will need to lie still on a bed that slides into the MRI tube for about 1 hour to obtain good images. This may be hard for some young children and they may need sedation so they can be calm or sleep through the process.

17. Why do you perform X-rays in addition to the MRI?

X-ray images (called radiographs) are necessary to evaluate whether the bones in the arms and legs are growing normally. The joints and limbs may become deformed in the presence of an osteochondroma. The legs may also be of different lengths. By taking X-rays at baseline and every 12 months, we can evaluate new or worsening deformities in the arms and legs.

It is also important to monitor the effect that palovarotene may have on growth plates throughout the MO-Ped Trial. Therefore, all study subjects will have X-rays of one knee and one hand/wrist at study screening and every 6 months during the 24-month treatment

period to monitor for both linear growth and any growth plate changes. Once the growth plates are completely closed at a body site, follow-up X-rays for that body part are no longer required.

Dual –X-ray absorptiometry (DXA) scans of the spine, one hip, and one radius will be performed at baseline and every 6 months to monitor bone thickness as part of safety monitoring.

18. Are there any risks for my child to be exposed to study procedures such as MRI, x-rays, DXA, or blood sampling?

Magnetic resonance imaging (MRI), x-rays, and blood sampling are important procedures needed to monitor the safety and efficacy of palovarotene during the MO-Ped Trial.

Risks related to these procedures are minimized when done by experienced personnel at study sites who are familiar with them.

There is no radiation exposure from the MRI scan. However, because children will have to lie still for up to 1 hour, it may be necessary to sedate your child. The risks of sedation will be explained during the enrollment process.

The radiation exposure of the x-rays and DXA (dual energy x – ray absorptiometry) represent minimal risk as they are well below the annual background radiation of 3 mSv (millisieverts, a measure of radiation dosage) in the US, and below the 5 mSv per year recommended by the US Food and Drug Administration (FDA).

19. Why is it necessary to live within a country that is hosting a MO-Ped Trial site?

As an investigational medicinal product, palovarotene can only be administered to human study subjects under special authorization by the national authorities within each country. Subjects must live in a country where the national authorities have approved the clinical study investigating palovarotene's use for the treatment of MO. This authorization is necessary to import palovarotene into the country and to perform home assessments within the country. Please look on www.clinicaltrials.gov (NCT03442985) for the most current information on clinical study sites and eligibility criteria.

20. How do I get to the clinical study site- Will my travel costs be reimbursed?

Clementia has hired a travel services company that specializes in clinical studies. All reasonable costs associated with participating in the MO-Ped Trial will be paid for by Clementia, including air flight travel, ground travel and accommodations for study subjects and a parent/caregiver. Travel to the study site is expected once every 6 months for examinations and assessments. Additional assessments are performed at home or if allowed, at a local medical facility between these study site visits.

21. Where are the targeted MO-Ped Trial sites?

We anticipate up to 30 international study sites across approximately 12 countries to enroll approximately 240 patients in total. Each site must receive national and local approval to

accept subjects. The time for these approvals may vary, so some sites would be open sooner than others.

The following are countries where sites are planned:
Australia
Belgium
Canada
France
Italy
Japan
Portugal
Spain
The Netherlands
Turkey
United Kingdom
United States