

MOVE TRIAL FAQs

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The MOVE Trial Summary

1. *What is the MOVE Trial?*

The MOVE Trial is a global, multicenter, open-label, Phase 3 confirmatory clinical study of palovarotene in fibrodysplasia ossificans progressiva (FOP) that is anticipated to enroll approximately 80 adults and children with FOP age 4 years or older. All subjects will take palovarotene every day (no placebo) for two years, with higher doses during times of flare-ups, to determine whether this dosing regimen of palovarotene reduces the formation of new heterotopic ossification relative to untreated subjects. The MOVE Trial will evaluate the safety and efficacy of palovarotene in FOP and complete the data package to be used in global regulatory applications for national approvals for palovarotene as a treatment in children and adults with FOP.

We encourage you to speak to your physician and one of the study physicians for the MOVE Trial regarding your potential enrollment in MOVE. You will also find key information on MOVE Trial on www.clinicaltrials.gov (NCT 03312634).

Palovarotene FAQs

2. *What is palovarotene?*

Palovarotene is an investigational medicinal product that Clementia is developing as an orally administered treatment for fibrodysplasia ossificans progressiva (FOP). Individuals with FOP have a mutated receptor in the bone morphogenetic protein (BMP) pathway that becomes overactive and sends signals that bring about the formation of heterotopic ossification (HO).

Palovarotene, a retinoic acid receptor gamma agonist (RAR γ), is thought to prevent HO in FOP due to its disruption of these signaling systems (in the BMP pathway). Preclinical studies in mouse models of FOP demonstrated that palovarotene blocked both injury-induced and spontaneous HO, maintained mobility, and normalized skeletal growth. Phase 2 dose ranging for palovarotene has been completed. In preliminary data analysis, a 97% reduction of new HO formation was observed in those subjects receiving daily palovarotene and increased dosing during a flare-up compared to untreated or placebo treated subjects. The Phase 3 MOVE Trial is being conducted to confirm these findings.

Palovarotene has been studied in over 800 humans, including healthy volunteers, people with emphysema, and individuals with FOP. Consistent with other retinoids, side effects involving the skin and mucous membranes (e.g. lining inside of your nose and mouth), including dry skin, dry lips, itching, rash, redness, mouth sores and hair loss have been reported at a higher rate in subjects treated with palovarotene compared to those treated with placebo (a sugar pill). In general, the number, intensity, and duration of these mucocutaneous and dermatologic events increased with increasing palovarotene dose. Most of these events were mild or moderate in intensity and generally resolved or improved after

treatment with skin lubricants, lip balms, antihistamines or decreasing the dose of palovarotene if necessary.

Palovarotene received Fast Track and Breakthrough Therapy designations from the US Food and Drug Administration (FDA) and Orphan designations for the treatment of FOP from both the FDA and the European Medicines Agency (EMA).

3. What is an Orphan designation?

Palovarotene's Orphan designation was granted by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in recognition that FOP is a rare, severely debilitating disease which currently lacks effective treatments.

More information on US Orphan designations can be found at <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>.

More information on EMA Orphan designations can be found at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp

4. What is a Fast Track designation?

Palovarotene's Fast Track designation was granted based on the US Food and Drug Administration's recognition of the serious nature of FOP and the potential that palovarotene could be beneficial in treating the disease.

More information on the Fast Track designations can be found at <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm>.

5. What is a Breakthrough Therapy designation?

Breakthrough Therapy is granted when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint. Palovarotene's designation was granted by the US FDA after evaluation of preliminary Phase 2 data. The primary intent of Breakthrough Therapy designation is to develop the data needed to support approval as efficiently as possible. More information on Breakthrough designation can be found at <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405397.htm>.

Phase 2 and Natural History Study FAQs

6. What is the Natural History Study (NHS)?

Clementia's NHS is an observational study that enrolled 114 FOP patients across the world. Subjects are evaluated annually for three years, with more frequent visits during a flare-up. The purpose of the NHS

is to understand the relationship between new bone formation and clinical measures of physical function and quality of life, and to monitor disease progression over time.

7. What were the Phase 2 studies?

Clementia's Phase 2 studies were interventional studies that evaluated four dosing regimens of palovarotene on several endpoints. The initial Phase 2 study was an adaptive, double-blind, placebo-control design. Subjects who completed the Phase 2 study had an option to enroll in an extension study: Part A of the extension continued the evaluation of the initial episodic dose regimen in which the dosing of palovarotene was started within seven days of a flare-up and continued for 6-weeks, and Part B introduced a chronic dose regimen in which palovarotene was taken daily and then given in higher doses at the time of flare-ups.

8. What is an adaptive study?

The US Food and Drug Administration provides a definition in its industry guidance document, <https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf>: "an adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."

9. What were the preliminary results of the Phase 2 program?

The full analysis of the Phase 2 program has not been completed, and the Part B extension is still ongoing. However, we observed from the pooled results of episodic, 6-week treatment (10 mg for 2 weeks followed by 5 mg for 4 weeks) of 47 flare-ups in the Phase 2 and Part A extension studies that palovarotene, relative to untreated flare-ups from the placebo group in the Phase 2 study and flare-ups from the NHS, reduced the percentage of subjects who developed heterotopic ossification (HO) after a flare-up by approximately 45% and decreased the volume of HO in those who formed HO by approximately 75%. Preliminary data analysis from the Part B extension study indicates that chronic dosing regimen of palovarotene with increased dosing at the time of a flare-up is more effective in suppressing HO, showing 97% reduction in HO volume when compared to untreated/placebo treated flare-ups. It is these data that support evaluating this dosing regimen in the Phase 3 confirmatory clinical study that is known as the MOVE Trial.

10. Are these Phase 2 data sufficient for regulatory approval?

The Phase 2 clinical studies were not intended to provide data that would be sufficient for regulatory approval. Rather it was a dose ranging program that evaluated various endpoints in FOP and several potential doses and dosing regimens of palovarotene. Its purpose was to inform the design of a Phase 3 study that would form the basis of global applications for regulatory approval. The Phase 2 program met its objectives and, along with the Natural History Study, provided important information necessary for

the design and implementation of the MOVE Trial, the Phase 3 confirmatory clinical study for palovarotene in FOP.

The MOVE Trial FAQs

11. What is the purpose of the Phase 3 confirmatory MOVE Trial and what are the clinical endpoints?

The MOVE Trial is a global, multicenter, open-label, Phase 3 confirmatory clinical study in approximately 80 adults and children with FOP over the age of 4 years. It is designed to evaluate whether an every day dosing regimen of palovarotene, combined with higher doses during times of flare-ups, will reduce the formation of new heterotopic ossification (HO) relative to the normal course of the disease.

As a confirmatory study, the MOVE Trial will evaluate the safety and efficacy of palovarotene in FOP for purposes of informing global regulatory applications for approval. The primary endpoint is the annualized change in new HO volume as measured by whole body computed tomography (WBCT). Secondary endpoints include the proportion of subjects with any new HO, change from baseline in the number of body regions with new HO, the proportion of subjects reporting flare-ups, and the flare-up rate per subject-month exposure.

As an open-label study, every subject will receive palovarotene over the full course of the study. There is no placebo group. The results for these 80 subjects will be compared to the data obtained in Clementia's Natural History Study (NHS).

As a global multicenter study, the MOVE Trial will be conducted at many sites across the world. Each site must obtain all relevant approvals from national and local authorities, so the sites will open for enrollment at different times. Please check at www.clinicaltrials.gov (NCT 03312634) for the latest on the MOVE Trial sites.

12. How long will the MOVE Trial last?

The MOVE Trial is designed for two years of treatment. That is, enrolled subjects will receive treatment with palovarotene for two years.

13. Who can participate in the MOVE Trial?

The MOVE Trial will enroll male or female subjects at least 4 years old weighing at least 10 kg who have a clinical diagnosis of FOP, the R206H ACVR1 mutation, and who live in a country with a MOVE Trial clinical study site. Four weeks must have elapsed since the end of the last flare-up before enrollment. Also, those of child-bearing age must be willing to comply with certain criteria that your principal investigator will explain. Additional exclusion criteria regarding medical history, medication use, allergies, and laboratory values are available at www.clinicaltrials.gov (NCT 03312634). Subjects participating in Clementia's NHS who meet the enrollment criteria can enroll into the MOVE study.

14. Why is it necessary to live within a country that is hosting a MOVE Trial site?

As an investigational product, palovarotene can only be administered to human subjects under special authorization by the national authorities within each country. Participants must live in a country in which the national authorities have approved the clinical trial investigating palovarotene's use for FOP. This authorization is necessary to import palovarotene into a country and to perform home assessments within the country. Please look on www.clinicaltrials.gov (NCT 03312634) for the most current information on clinical trial sites and eligibility criteria.

15. Where are the targeted MOVE Trial sites?

We anticipate the MOVE Trial will be conducted at 20 sites in 16 countries across the world. Each site must apply for national and local approvals. The application and approval process may take more time in some places, leading to some study sites enrolling into the trial before other sites are ready. As soon as a site is ready to enroll, Clementia will update the list on www.clinicaltrials.gov (NCT 03312634) and communicate this information to the community.

The specific countries in which sites are planned are:

- Argentina
- Australia
- Brazil
- Canada
- France
- Germany
- Italy
- Japan
- Russia
- South Africa
- South Korea
- Spain
- Sweden
- The Netherlands
- United Kingdom
- United States

16. What if a subject enrolled in the MOVE Trial experiences side effects to the treatment?

Side effects are monitored throughout the study. Any subject who experiences a side effect during the clinical study will be evaluated by the principal investigator and site staff and treated appropriately. In addition, the study physicians may decrease the dose of palovarotene or temporarily or permanently stop drug treatment. All subjects have the option to stop their participation at any time.

Known potential side effects will be described in the informed consent, which is a detailed document that is discussed during a meeting with the study physician, clinical study staff, and the prospective subject during the enrollment evaluation. This is an opportunity to discuss any questions regarding the MOVE Trial, including potential health risks.

17. Why was whole body computed tomography (WBCT) chosen to measure heterotopic ossification (HO) in the MOVE Trial?

Information obtained from Clementia's Natural History Study demonstrated that whole body computed tomography (WBCT) is a sensitive imaging modality that can document the presence and quantity of existing and new HO. By using this modality at regular intervals, it decreases the burden on study subjects as they do not need to travel to the clinical site at the time of a flare-up.

18. How is MOVE different from the previous studies?

The MOVE Trial is a Phase 3 confirmatory clinical study that was developed based on information obtained from Clementia's Phase 2 and natural history studies. Its goal is to determine whether palovarotene can safely prevent and/or minimize new heterotopic ossification (HO). The MOVE Trial incorporates the following changes compared to the Phase 2 program:

- The MOVE Trial does not require a placebo group: all subjects will be treated with palovarotene.
- The MOVE Trial uses chronic dosing for palovarotene with increased dosing at the time of a flare-up in all subjects, both children and adults: this dosing regimen provided the best efficacy in the Phase 2 program.
- The MOVE Trial enrolls subjects at their usual state of health and not at the time of a flare-up.
- The MOVE Trial does not require a visit to the clinical study site at the time of a flare-up.
- The MOVE Trial is using more clinical trial sites worldwide than previous studies and only patients living in a country that has a MOVE Trial clinical study site are eligible.

19. Are subjects who participated in the Phase 2 program able to enroll in the MOVE study?

No, the enrollment into the MOVE Trial is limited to subjects who have not participated previously in one of the palovarotene treatment trials. However, the ongoing Phase 2 open-label study is being amended so that all subjects (including children) can receive the chronic/flare-up dosing regimen and will no longer need to travel to the clinical site at the time of a flare-up, with the efficacy determined by whole body CT scans.

Subjects participating in Clementia's Natural History Study who meet the enrollment criteria can participate in the MOVE Trial.

20. Why is a placebo not being used in MOVE?

All subjects in the MOVE Trial will receive palovarotene. Placebo will not be used in the MOVE Trial. Good scientific and medical research requires a control group for comparison with the active treatment

group. This is often accomplished through the use of a placebo control group. However, in certain situations, regulatory authorities allow data from other sources to be used in place of a placebo control. Given the serious and devastating effects of HO for individuals with FOP and Clementia's existing well designed and comprehensive Natural History Study (NHS) that yielded important information on the natural course of FOP in untreated subjects, relevant regulatory authorities determined that data obtained from subjects in Clementia's NHS can serve as an appropriate control for the MOVE Trial.

21. What is the dosing for palovarotene in MOVE Trial and how does this compare with previous studies?

Our Phase 2 program was designed to inform the optimal palovarotene dose regimen that would then be further evaluated in the MOVE Trial, the Phase 3 confirmatory clinical study for palovarotene in FOP. We studied four different palovarotene dosing regimens that included flare-up only and chronic/flare-up dosing schedules. The Phase 2 results to date have demonstrated that palovarotene dosed chronically at 5 mg once daily, with dosing increased to 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks during flare-up activity, provides the optimal dosing for preventing or minimizing new heterotopic ossification relative to untreated subjects. The dose is adjusted for weight in children who are still growing.

22. How do I get to the clinical study site – will my travel costs be reimbursed?

Clementia has hired a travel services agent that is specialized in assisting with clinical studies. All reasonable costs associated with participating in this study will be paid for by Clementia, including travel and accommodations for you and a caregiver. Travel to the investigational site is expected once every six months for examinations and assessments, with home assessments performed between clinic visits.

23. Will participants in the MOVE Trial be able to receive their usual care?

Yes, although the clinical study protocol does not allow some medications because of potential interactions with palovarotene, it is permissible to use standard of care FOP treatments like prednisone, non-steroidal anti-inflammatory medications, and oxygen for instance. The clinical study personnel will discuss this information with you during the screening process.

As skin and mucous membrane reactions are the most common side effects associated with treatment with palovarotene, a specific leaflet describing recommended treatment and steps that can be taken to prevent or minimize these side effects will be provided to each subject at the initiation of study treatment.

24. Are there potential risks of administering palovarotene to children who are still growing?

The process by which palovarotene prevents heterotopic ossification may also impact long bones of growing children. Monitoring of the growth plate and linear growth in children has not demonstrated treatment-related effects of palovarotene following flare-up based dosing to date. As palovarotene will be administered daily, with higher doses during a flare-up to all subjects enrolled in the MOVE Trial, all

subjects under the age of 18 years who are still growing will have x-rays of the knee and hand/wrist performed every six months to monitor for potential treatment-related effects.

25. If I do not qualify for the MOVE Trial, is there any other way to get treated with palovarotene?

At present, the only way to obtain palovarotene is as a subject in the MOVE Trial. We are evaluating options for making palovarotene available outside of a clinical study and will let the community know when that happens and for what circumstances.

26. What about the surgical excision trial?

Clementia has convened a panel of experts to advise in the design and execution of the surgical excision trial, called the REMOVE trial. This study is still in the planning stages, and further information will be provided in the future.