CLINICAL STUDY RESULTS

A Study to Learn about the Effects of Palovarotene in People with Fibrodysplasia Ossificans Progressiva (FOP)

The results of this study suggest that a higher dose and long-term therapy with palovarotene should be considered to treat FOP.

The results shown in this summary are from one clinical study. Other clinical studies may produce different results.

What was the study about?

Palovarotene is developed to treat a disorder called Fibrodysplasia Ossificans Progressiva (FOP), where the soft tissues like muscles and ligaments are replaced by bone. People with FOP can experience painful swellings called **flare-ups** which often lead to the formation of new bone in the soft tissues. This can cause physical disability over time.

Palovarotene works by blocking certain chemical signals that cause bone formation.

The aim of this study was to learn if palovarotene is safe and effective in reducing the formation of bone in the soft tissues of participants with FOP.

The study took place between October 2014 and September 2022 at 8 study sites around the world.

This was an "open-label" study, which means that both researchers and participants knew what participants were receiving.

This study was divided into 3 parts:

Part A included participants (adults and children) with FOP from a previous study (PVO-1A-201) who were observed for a year.

During Part A, each participant could receive palovarotene treatment for up to a maximum of two, new distinct flare-ups.

Part B included participants from Part A and new adult participants with FOP. They were treated and followed up for 2 years.

Adult participants were given a low-dose long-term (chronic) treatment of palovarotene throughout Part B. If a flare-up occurred in any participant, they were given a higher dose (flare-up treatment). Once the flare-up resolved, chronic treatment was resumed.

Child participants all received flare-up treatment adjusted according to their weight. They did not receive the chronic treatment.

Part C included participants from Part B. No new participants with FOP entered Part C. Participants were treated and followed up for 4 years.

All participants, including children, received chronic treatment. If a flare-up occurred, flare-up treatment was given. Once the flare-up resolved, chronic treatment was continued.

The dose was reduced if the participant experienced side effects.

What treatments were used?

Palovarotene capsules were given by mouth with the following dose and timings	
PART A	**PART B AND PART C**
Flare-up treatment 10 mg daily for 2 weeks followed by 5 mg daily for 4 weeks. 	**Chronic treatment*** 5 mg daily. **Flare-up treatment** 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.

* Child participants did not receive chronic treatment in Part B.

Who took part in this study?

Participants were eligible to take part in the study if they:

- had completed the previous study 'PVO-1A-201' or were adults with a gene that causes FOP,
- had FOP flare-ups, and
- were aged between 6 and 65 years.

Participants were not eligible to take part in the study if they:

- weighed less than 20 kg,
- took any medicine that interferes with palovarotene, or
- had any health condition making them unfit for the study as per the study doctor.

	Number of participants	Average age (years)	Male (%)	Female (%)
Part A	40	22	18 (45%)	22 (55%)
Part B	54	21	23 (43%)	31 (57%)
Part C	48	21	23 (48%)	25 (52%)

What researchers found out in the study?

In this study researchers found that:

- the percentage of flare-ups that did not form bone increased after 12 weeks of treatment, and
- the amount (volume) of new bone formation per year decreased after treatment.

What percentage of flare-ups did not form bone within the soft tissue after 12 weeks of treatment?

Researchers counted the number of flare-ups that did not form new bone within the soft tissue. They compared the percentages of flare-ups that formed new bone at the start of the study and after 12 weeks of palovarotene treatment.

64% of flare-ups in Part A and 73% of flare-ups in Part B did not form bone within the soft tissue after 12 weeks of treatment.

What was the amount of new bone formation at Week 6 and Week 12 of treatment in Part A?

The average amount of new bone formation was 1735 mm^3 at Week 6 and 2310 mm^3 at Week 12 of treatment in Part A.

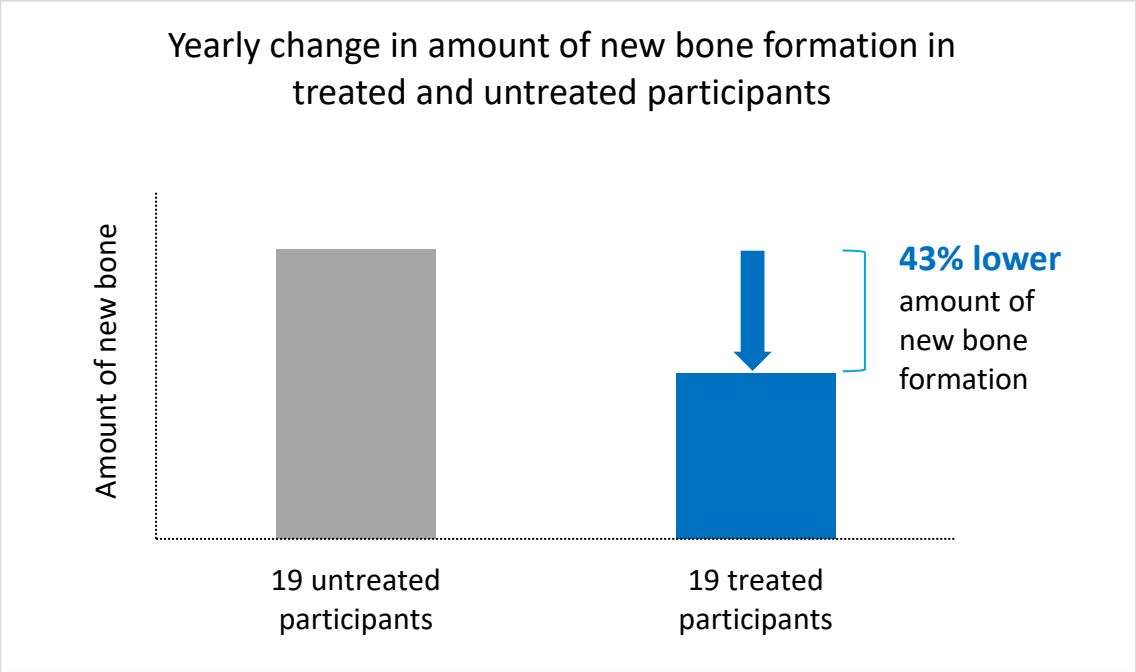
What was the amount of new bone formation at Week 12 in Part B?

The average amount of new bone formation was 4818 mm^3 at Week 12 of treatment in Part B.

What was the yearly change in the amount of new bone formation within soft tissue in participants who took palovarotene compared to those who did not?

In Part C, researchers measured the amount of new bone formation per year in the entire body (except the head) in participants who were treated and compared it with those who were not treated. Researchers compared results of 19 treated participants from this study with 19 untreated participants from an earlier Ipsen study.

The average amount of new bone formation within soft tissue per year was 16,120 mm^3 in participants who took palovarotene and 28,428 mm^3 in participants who did not. The average difference was 12,308 mm^3, or 43% lower, in the palovarotene treated participants.



How did the treatment make participants feel?

During clinical studies, participants are asked to report if they feel unwell, experience any kind of medical event, or notice anything different about their bodies. These are called 'adverse events.' Researchers record all adverse events reported by participants, whatever the cause.

If the study doctor thinks an adverse event may be related to the study treatment, it is called a 'side effect' or a 'treatment-related adverse event'. An adverse event or side effect is considered 'serious' when it is life-threatening, causes lasting problems, or leads to hospitalisation.

- Adverse events that are *life-threatening*, cause lasting problems or require an individual to go to the hospital are considered serious.
- 8 participants in this study experienced serious side effects.
- No participants died during the study.

In Part A, no participants experienced a serious side effect.

In Part B, 2 out of the 54 participants did not receive the study treatment. Therefore, side effects were reported for 52 participants.

2 out of 52 participants experienced serious side effects in Part B. One participant experienced **injury to bones of the ankle joint** (ankle fracture) and another experienced **worsening of flare-ups*** (condition aggravated).

In Part C, 2 out of the 48 participants did not receive the study treatment. Therefore, side effects were reported for 46 participants.

6 out of 46 participants experienced serious side effects in Part C. The following serious side effects were experienced by one or more participants:

- **Extreme response to an infection** (Staphylococcal sepsis)
- **Diarrhea**
- **Early growth plate closure** (Epiphyses premature fusion)
- **Fits** (Seizure)
- **Infection in the stomach and intestines** (Gastroenteritis)
- **Lung infection** (Pneumonia bacterial)
- **Pain in lower legs or hands** (Pain in extremity)
- **Skin infection** (Cellulitis)
- **Skin redness** (Erythema)
- **Swelling in lower legs or hands** (Peripheral swelling)
- **Vomiting**
- **Worsening of flare-ups*** (Condition aggravated)

* Flare-ups that did not meet the condition to be treated with Palovarotene.

Not all the side effects reported were serious. The overall side effects and their numbers are as follows:

In Part A, 18 out of 20 participants (90%) who received flare-up treatment experienced side effects.

The most common side effects that happened in more than 25% of the participants are shown in the table below. They are shown as a percentage (%) followed by the actual number of participants in the group (for example, 1 out of 15 or 7%).

Side Effects	Flare-up treatment (20 Participants)
Dry skin	75% (15 out of 20) 
Dry lips	65% (13 out of 20) 
Itching	35% (7 out of 20) 

In Part B, 51 out of 52 participants (98%) who received flare-up treatment or chronic treatment experienced side effects.

The most common side effects that happened in more than 30% of the participants are shown in the table below.

Side Effects	Flare-up or chronic treatment (52 Participants)
Dry skin	83% (43 out of 52) 
Dry lips	62% (32 out of 52) 
Itching	54% (28 out of 52) 
Hair loss	48% (25 out of 52) 
Rash	44% (23 out of 52) 
Skin peeling	42% (22 out of 52) 
Skin redness	42% (22 out of 52) 
Itching all over the body	40% (21 out of 52) 

In Part C, 43 out of 46 participants (93%) who received flare-up treatment or chronic treatment experienced side effects.

The most common side effects that happened in more than 30% of the participants are shown in the table below.

Side Effects	Flare-up or chronic treatment (46 Participants)
Dry skin	63% (29 out of 46) 
Skin peeling	33% (15 out of 46) 

More information

To learn more about this study, please visit the ClinicalTrials.gov website and search for study NCT02279095.

For more information about current treatments available, please speak to your healthcare provider. If you have any questions about this study, please contact the sponsor, Ipsen at:

clinical.trials@ipsen.com

Future research

Currently, a study called PIVOINE is ongoing to continue to ensure that palovarotene is safe and available to those who participated in the study described here (or any other 'parent' studies like PVO-1A-301 or Study PVO-1A-204) and who could benefit from the treatment according to their study doctor.

Study identification and other information

Full study title: A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RARγ Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).

STUDY NUMBERS: Europe: 2014-002496-28 | United States: NCT02279095 |

Protocol: PVO-1A-202.

OTHER INFORMATION: Phase II studies can take several months or years to complete and look at how safe a potential new treatment is. Some changes were made during the study to ensure safety, improve recruitment, make having the medicines easier, and clarify information in the study protocol (i.e., the researcher's guide to the study).

We thank all the volunteers who took part in this study. Without their support, advances in treatments for medical conditions would not be possible.

We would also like to thank the people who took the time to review this document to make it easier for a general audience to read.