CLINICAL STUDY RESULTS

A study to learn about long-term effects and safety of odevixibat in children with progressive familial intrahepatic cholestasis types 1 and 2 (PEDFIC 2)

Overall, the results of this study suggest that long-term treatment with odevixibat reduced the level of bile acids and itching symptoms. No major safety issues were reported with odevixibat.

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

This lay summary was created by Ipsen with the assistance of a third-party writing service provider.

What was the study about?

This study assessed the long-term effects and safety of odevixibat in participants with progressive familial intrahepatic cholestasis (PFIC), most of whom were children, in a study called PEDFIC-2.

PFIC is a rare inherited disorder that causes progressive liver disease, mostly in children. Bile acids are substances produced by the liver and released into the intestine, where they help with digestion of food. The remaining bile acids are then absorbed from the intestine and return to the liver. In people with PFIC, the release of bile acid from the liver and its movement around the body do not work normally. The liver continues to produce bile acid, but it is not properly removed from the body. This causes the bile acids to build up in the liver over time.

Excess bile acids in the liver cause damage to liver cells. This can stop the liver from working properly and even lead to liver failure. Children with PFIC typically experience poor growth, vitamin deficiencies, and intense itching. The itching can be so severe that it disrupts sleep and affects the quality of life for the children and their families. The 3 main subtypes of PFIC are type 1, type 2, and type 3.

Odevixibat is a medication which is approved for the treatment of PFIC in the European Union, the United Kingdom, Canada, countries in Latin America, and Asia. In the United States, odevixibat is approved for the treatment of itching associated with PFIC. When taken by mouth, odevixibat helps lower bile acids in the body by preventing the intestines from absorbing them again. This means that instead of being returned to the liver, these bile acids are eliminated through the stool. This reduces the build-up of bile acids in the liver and lowers the amount of bile acids in the bloodstream.

Previously, treatment for PFIC was limited to treating the symptoms, and surgery to lower the level of bile acids. However, these treatments do not work for everyone, and some patients will require a liver transplant.

The aim of this study was to learn about the long-term effects of odevixibat on the level of bile acids in the blood, and on itching symptoms, in participants with PFIC.

The study took place between September 2018 and December 2025 at 32 sites in Europe (Belgium, France, Germany, Italy, Netherlands, Poland, United Kingdom), United States, Australia, Canada, Israel, Saudi Arabia and Turkey.

Who took part in this study?

116
PARTICIPANTS

64
MALES

52
FEMALES

6 YEARS
AVERAGE AGE

Participants could take part in this study if they:

Group 1:

- had PFIC type 1 or PFIC type 2, and
- completed 6 months of treatment in a previous study in children (A4250-005), or withdrew early from A4250-005 after 3 months of odevixibat treatment due to unmanageable symptoms

Group 2:

- had not participated in Study A4250-005
- were any age and had any type of PFIC
- had worsening of disease with increased level of bile acids in the blood as decided by the study doctor
- had history of intense itching

Participants or their caregivers agreed to complete an electronic diary (e-diary) to record daily treatment and symptoms and related questions.

Participants could not take part in the study if they had a history of certain medical conditions or liver disease, and

Group 1:

- failed to follow treatment with odevixibat in Study A4250-005

Group 2:

- had a liver transplant, or a planned liver transplant within 6 months

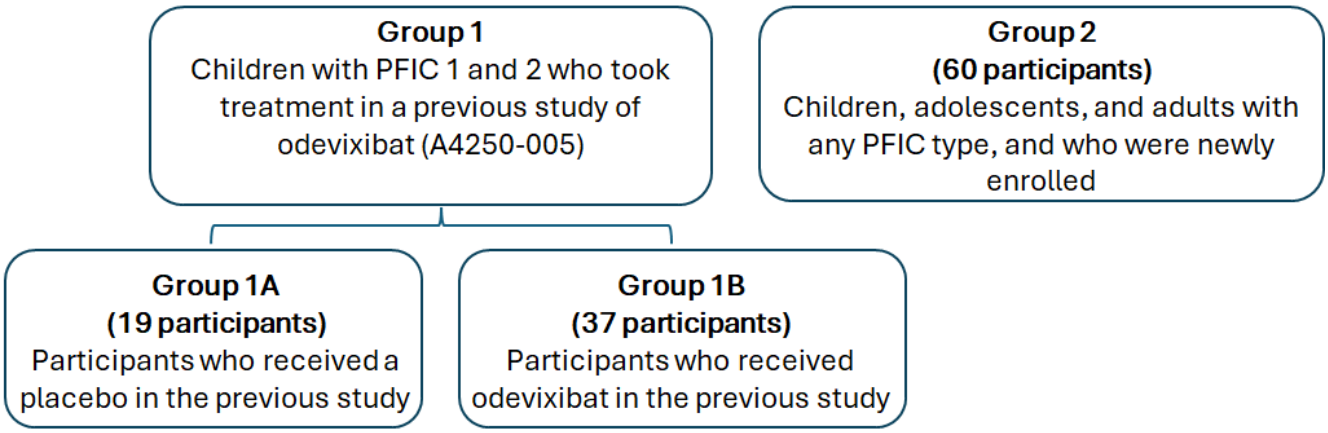
What treatments were used?

Odevixibat capsules at doses of 40 micrograms (µg)* or 120 µg for every kilogram (kg) of body weight, taken by mouth once daily.

*Some participants in Group 2 took odevixibat 40 µg/kg for the first 12 weeks of the study. After 12 weeks, the dose could be increased to 120 µg/kg as per the study doctor's assessment.

This was an open-label study, which means that the researchers and the participants knew which treatment participants were taking.

- This study had 2 groups – **Group 1** and **Group 2**.
- **Group 1** was further divided into **Group 1A** and **Group 1B**.



A placebo looks like the study treatment and is given in the same way but does not have any medicine in it. Researchers sometimes use a placebo to understand if the changes seen were due to the study treatment or if they happened by chance.

In this study, all participants took odevixibat capsules by mouth.

The study was divided into 4 parts:

Screening period (2 months): Participants in **Group 1** were directly enrolled from the previous study (A4250-005). For **Group 2**, researchers checked if new participants could take part in the study.

Treatment period (72 weeks, which is around 1 and a half years): Of the 116 participants, 111 started taking odevixibat 120 µg/kg once daily. The remaining 5 participants (all in Group 2) started with odevixibat 40 µg/kg once daily for the first 12 weeks. Participants who could not tolerate the dose of 120 µg/kg were allowed to take odevixibat 40 µg/kg after the study doctors' assessment.

On the first day of treatment, participants and participants' caregivers were given an e-diary. They recorded their daily treatment, itching and scratching symptoms, and sleep quality patterns in the e-diary. This was done twice daily for the first 6 months, and then twice daily for the 3 weeks before each clinic visit, thereafter until the 1 and a half years treatment period ended.

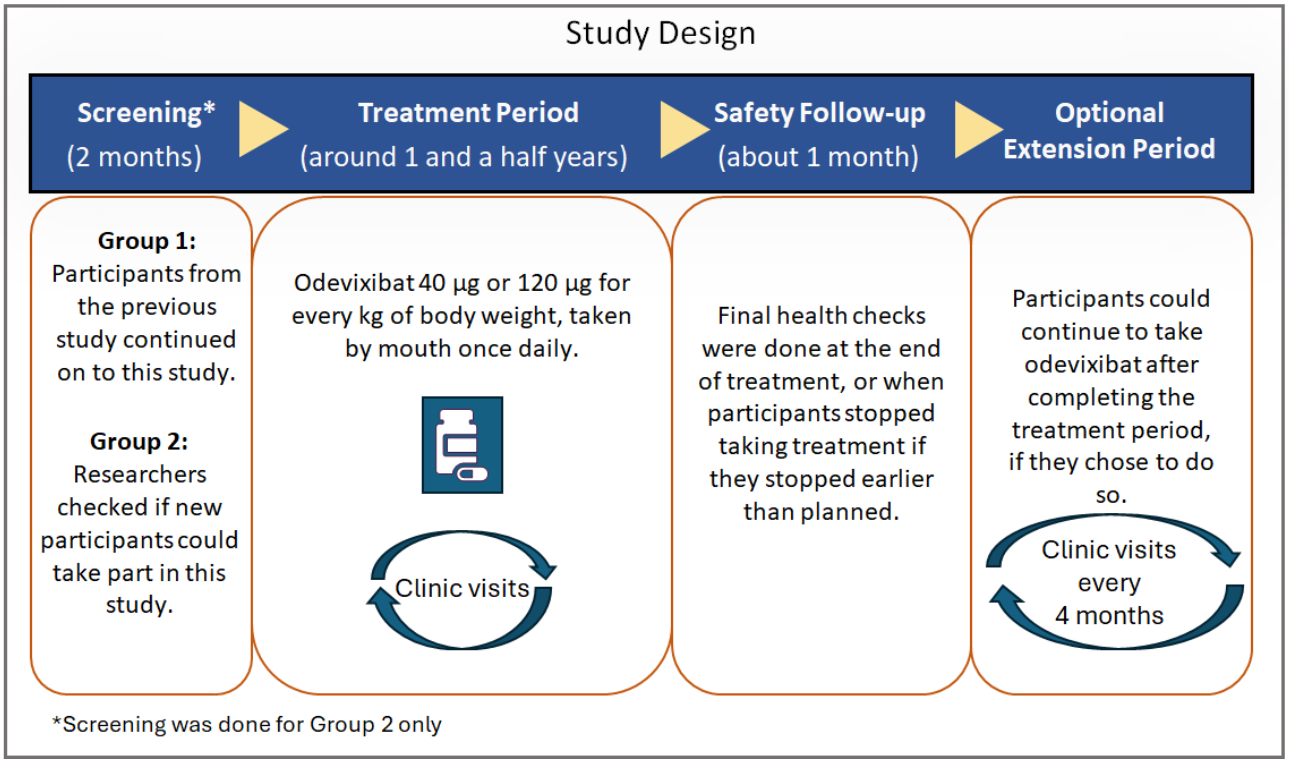
After the first dose of odevixibat, participants/caregivers returned to the clinic during Week 4 and Week 12, and then every 10 to 12 weeks for health check-ups until the end of the 1 and a half years treatment period. Researchers connected with participants/caregivers through phone calls between the visits to check on the participants' health.

Safety follow-up period (about 1 month): Participants had to visit the clinic around 1 month after their last dose of odevixibat. Participants were given the option to continue odevixibat at the end of 1 and a half years treatment period (treatment extension period), and those who chose to continue did not have to attend this follow-up visit.

All participants' health was checked and assessed at the end of treatment, even if they discontinued the treatment early.

Optional treatment extension period: Participants who chose to continue odevixibat treatment after the end of the 1 and a half years study treatment period visited the clinic every 4 months for health check-ups until odevixibat was commercially available.

The figure below shows the study design:



What were the results of the study?

Participants who took odevixibat for 1 and a half years had reduced levels of bile acids in the blood and improvement in itching symptoms.

Was there a change in the level of bile acids in the participants' blood after around 1 and a half years of treatment with odevixibat in this study?

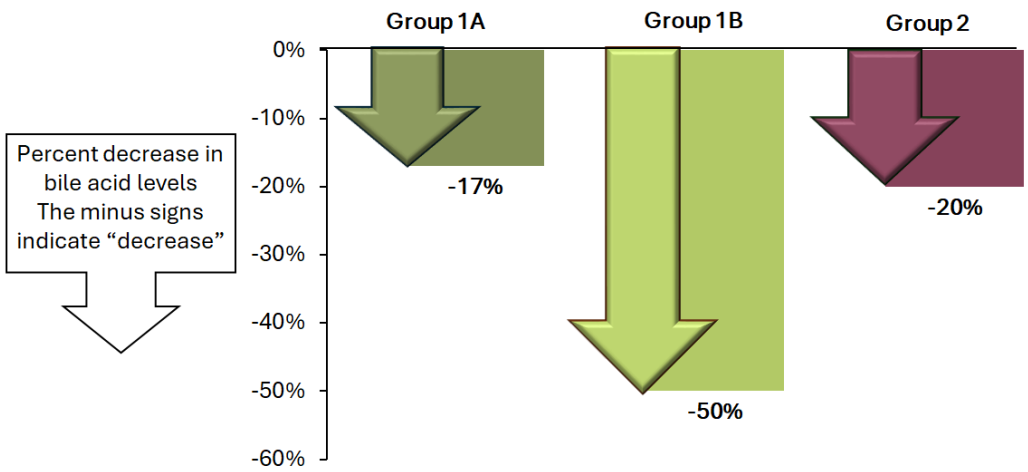
Measuring the level of bile acids in the blood is a common way to monitor people with PFIC. Higher levels of bile acids generally indicate worsening of PFIC.

To answer this question, results were available for 15 participants in **Group 1A**, 28 participants in **Group 1B,** and 43 participants in **Group 2**.

- Note: for participants in **Group 1B** who took odevixibat in the previous Study A4250-005, the starting bile acid levels, that is, before any treatment with odevixibat during A4250-005 were used for analysis of the result.
- For patients who had not received odevixibat before, that is, for those in **Group 1A** who took a placebo in the previous Study A4250-005 and those in **Group 2**, the starting bile acid levels from this study were used for analysis of the result.

Bile acid levels in participants decreased by an average of 17% in **Group 1A**, by 50% in **Group 1B**, and by 20% in **Group 2**. Participants in **Group 1B**, who had already taken odevixibat in the previous Study A4250-005, showed a greater decrease in bile acid levels.

Change in level of bile acids after around 1 and a half years of treatment in this study



How many participants experienced a reduction in itching and improvement in scratching symptoms after around 1 and a half years of treatment, based on participants' caregivers reported outcomes?

To answer this question, results were available for 12 participants in **Group 1A**, 26 participants in **Group 1B,** and 31 participants in **Group 2**.

Taken as averages across each group, 55% of participants in **Group 1A**, 39% in **Group 1B**, and 77% in **Group 2** showed improvement in severity of itching and scratching symptoms during the 1 and a half years treatment period.

Other study results:

How many participants underwent surgery to redirect the flow of bile acids in the body, or underwent a liver transplantation?

Up to the end of the study, 3 participants underwent surgery to redirect the flow of bile acids in the body, and 17 participants underwent a liver transplantation.
One participant had surgery to redivert bile acid flow before receiving a liver transplant.

What impact did odevixibat have on participants' growth compared to standard growth measures in height, weight, body mass index, and arm circumference at the end of the study?

Children with PFIC have difficulty absorbing fats, which may make it harder for them to grow and develop. In this study, on average participants in all groups got taller and gained weight at a better rate after treatment with odevixibat, compared to before treatment.

How did the treatment affect people taking it?

During the study, participants and their caregivers were asked to report any 'adverse events', that is, if they felt unwell, experienced any kind of medical event, or noticed anything different about their bodies. Researchers recorded all adverse events reported by participants, whatever the cause. For example, some participants caught COVID-19 and this was reported as an adverse event, although it was not related to odevixibat.

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

- 2 participants experienced a serious side effect of diarrhoea.
- No participants died during the study.

Overall, 41% (47 out of 116) of participants experienced at least 1 side effect.

The most common side effects, which happened in at least 4 out of 116 participants, are shown below.

The most common side effects were diarrhoea, increases in bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in the blood:

- Bilirubin is a yellowish substance formed by the breakdown of red blood cells. An increase in levels of bilirubin in the blood may indicate liver problems.
- ALT and AST are proteins produced by the liver. An increase in levels of ALT or AST in the blood may indicate damage to liver cells.

Side Effects	Group 1 (56 Participants)		Group 2 (60 participants)	All 116 participants
	Group 1A (19 participants)	Group 1B (37 participants)		
Any side effects	42% (8 participants)	46% (17 participants)	37% (22 participants)	41% (47 participants)
Diarrhoea	0	11% (4 participants)	17% (10 participants)	12% (14 participants)
Increase in bilirubin	11% (2 participants)	16% (6 participants)	10% (6 participants)	12% (14 participants)
Increase in ALT	11% (2 participants)	3% (1 participants)	7% (4 participants)	6% (7 participants)
Increase in AST	5% (1 participant)	0	5% (3 participants)	3% (4 participants)

4% (5 out of 116) of participants stopped taking odevixibat treatment because of side effects.

More information

To learn more about this study, please visit:

- ClinicalTrials.gov and search for study NCT03659916 or
- Clinicaltrialsregister.eu/ctr-search/search and search for study 2017-002325-38.

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

There is no future clinical research planned on this topic.

Study identification and other information

FULL STUDY TITLE: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2).

STUDY NUMBERS: Europe: 2017-002325-38 | United States: NCT03659916

PROTOCOL: A4250-008

OTHER INFORMATION: Phase 3 studies can take several months to years to complete and look at how safe and/or effective a potential new treatment is.

We thank all the people with PFIC who took part in this study and their families and caregivers. 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.