Clinical Trial Results – Layperson Summary

A study of peginterferon alfa-2a plus lamivudine or entecavir in children and adolescents with immune-tolerant chronic hepatitis B[1]

Thank you to the people who took part in this study

The people who took part have helped clinical researchers to answer important questions about the treatment of children and adolescents with immune-tolerant chronic hepatitis B.

About this summary

This is a summary of the results of a clinical study written for:

- people who took part in the study
- family members and guardians of children who took part in the study and
- members of the public.

This summary is based on the information known at the time of writing (August 2020)

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine. This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.

Contents of the summary

[1]See the end of the summary for the full title of the study.

1. General information about this study

Why was this study done?

Hepatitis B is a serious liver infection caused by hepatitis B virus (HBV). In some people, hepatitis B is a long-lasting or "chronic" condition that can lead to liver damage.

In people living with chronic hepatitis B, the virus lives inside liver cells and makes copies of itself. When this happens, parts of the virus are released into the blood. In some people, the immune system attacks cells infected with HBV. This reaction can damage the liver.

As for other infections, if the immune system starts making antibodies against the virus it means that the person's immune system is fighting the infection.

Children infected with HBV at birth develop "immune-tolerant chronic hepatitis B". In these children, the immune system does not eliminate the virus and it keeps making copies of itself. As a result, there are high levels of virus particles in the blood.

Doctors generally do not treat people with immune-tolerant chronic hepatitis B with medicines. Instead, they check these people often and start treatment only after they notice that damage to the liver is happening.

In this study clinical researchers wanted to see if treatment with two types of medicine could make the immune system start fighting the virus in children and adolescents with immune-tolerant chronic hepatitis B.

What are the study medicines?

Peginterferon alfa-2a
You say this as "peg-IN-ter-FEER-on AL-fa too-ay".

- Peginterferon alfa-2a is a type of medicine given by injection that works by helping the body's natural defences (immune system) fight infection.

Antiviral medicines (entecavir and lamivudine)

- **Entecavir**
  - You say this as "en-TEK-ah-veer".
- **Lamivudine**
  - You say this as "la-MIV-ue-deen".
- Entecavir and lamivudine are medicines that are taken by mouth. They work by sticking to a protein inside infected liver cells. This means that the virus cannot be copied.

What did researchers want to find out?

- Clinical researchers did this study to find out how effective the study medicines (peginterferon alfa-2a plus an antiviral) were, compared with no treatment (monitoring) (see section 4, "What were the results of the study?"). This was done by measuring specific parts of the virus in the blood called HBV DNA, hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg).
- They also wanted to find out how safe this combination of medicines was, by checking how many people had side effects when taking peginterferon alfa-2a plus an antiviral medicine (see section 5, "What were the side effects?").

The main questions that clinical researchers wanted to answer was:
In children and adolescents aged 3 to <18 years with immune-tolerant chronic hepatitis B, can treatment with peginterferon alfa-2a plus an antiviral medicine prompt the immune system to start fighting HBV infection?

In particular, does treatment result in the disappearance of virus particles called HBsAg from the bloodstream?

Other questions that clinical researchers wanted to answer included:
Does treatment result in the disappearance of virus particles called HBeAg from the bloodstream?
Does treatment result in the production of antibodies against HBsAg?
Does treatment result in the production of antibodies against HBeAg?
Does treatment decrease the amount of virus particles called HBV DNA in the bloodstream?
Does treatment result in the production of antibodies against HBeAg and decrease the amount of HBV DNA in the bloodstream?

What kind of study was this?

This was a 'Phase 3' study. This means that peginterferon alfa-2a and an antiviral medicine (entecavir and lamivudine) had already been tested in people with chronic hepatitis B before this study.

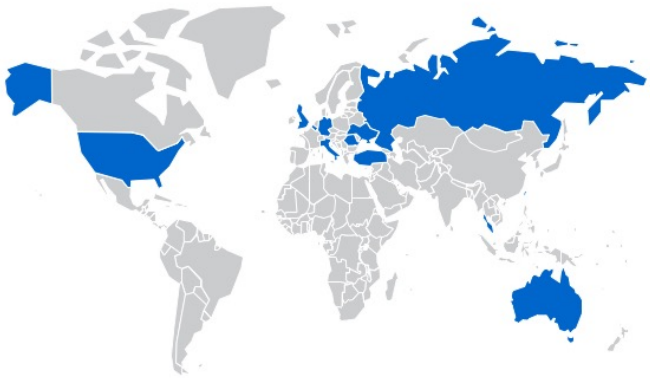
Children and adolescents taking part in this study took either peginterferon alfa-2a and an antiviral medicine (either entecavir or lamivudine), or they received no treatment, but were checked frequently by doctors – this was to find out if treatment with peginterferon alfa-2a and an antiviral helped the immune system to start fighting HBV infection.

The study was 'randomised'. This means that it was decided by chance whether a study participant received medicine or was checked frequently but did not receive treatment in the study.

When and where did the study take place?

The study started in February 2007 and ended in January 2020. This summary includes the final results.

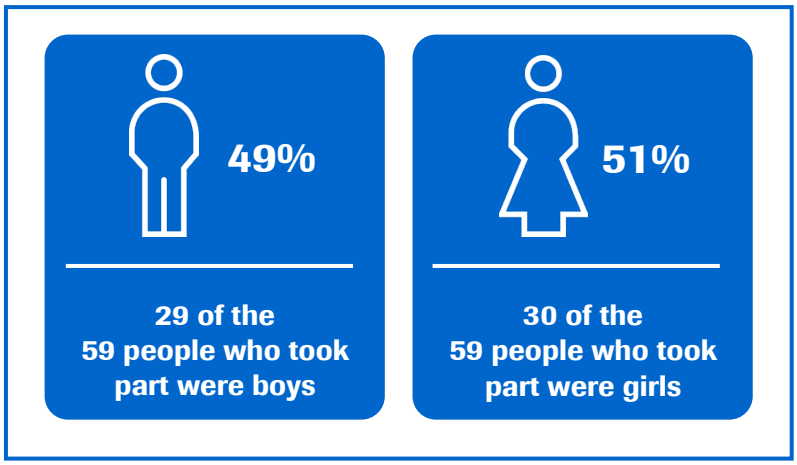
The study took place at 22 study centres across 12 countries and territories in Asia, Europe, North America and Oceania. The United Kingdom (31%), Turkey (25%) and the United States (12%) were the countries with the highest number of people enrolled. The following map shows all the countries where the study took place.



- Australia
- Belgium
- Germany
- Italy
- Malaysia
- Romania
- Russian Federation
- Taiwan
- Turkey
- Ukraine
- United Kingdom
- United States

2. Who took part in this study?

Fifty-nine children and adolescents with immune-tolerant chronic hepatitis B took part in this study. More information on the people who took part is given below.



People could take part in this study if they:

- Were boys or girls
- Were aged 3 to <18 years
- Had immune-tolerant chronic hepatitis B
- Resided in a country or territory listed above

People could NOT take part in this study if they:

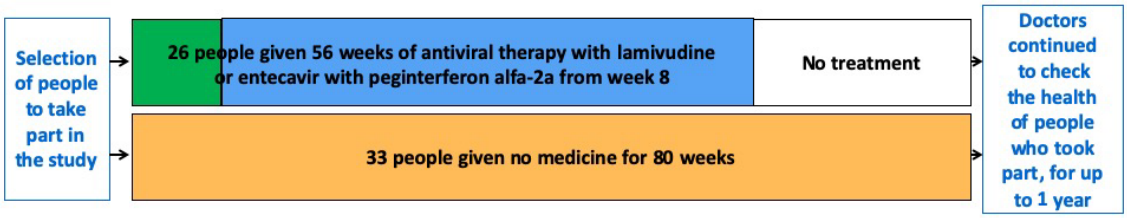
- Had HIV
- Had certain health problems including liver disease due to causes other than hepatitis B virus infection

3. What happened during the study?

During the study, people were selected randomly to get treatment or no treatment. The assignment to the study groups was performed by a computer.

The study groups were:

- An antiviral medicine (either **lamivudine** or **entecavir**) taken orally as a tablet once a day for 8 weeks on its own. Then **peginterferon alfa-2a** injected under the skin once a week plus daily **lamivudine** or **entecavir** for 48 weeks. Patients were then checked frequently for 1 year after the end of treatment. Each patient's doctor decided if a patient would receive **lamivudine** or **entecavir**.
- **Checking frequently without medicines for 80 weeks**.



In this study, 26 people were selected to be treated with peginterferon alfa-2a plus an antiviral and 33 people were selected to be checked frequently without treatment. At the start of the study 3 people were selected to be treated with peginterferon alfa-2a alone. This group is not included in this summary because it was decided not to enrol more patients in this group.

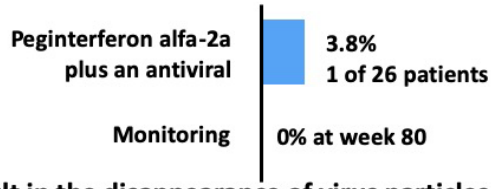
This study was supposed to recruit more people and continue for 5 years after the end of treatment. However, while the study was in progress, the results of two other similar studies were released in October 2017. These studies showed that treatment of adults or children with peginterferon alfa-2a plus entecavir did not help the immune system to start fighting HBV infection. Based on these studies and a recommendation by the Data Safety Monitoring Board for this study, F. Hoffmann La Roche amended the plan for this study in March 2018:

- No more people would be enrolled.
- Follow-up after treatment would be 1 year rather than 5 years.

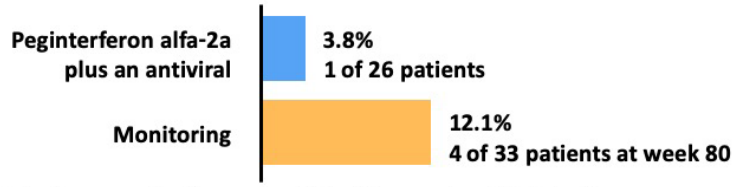
4. What were the results of the study?

In children and adolescents with immune-tolerant chronic hepatitis B, can treatment:

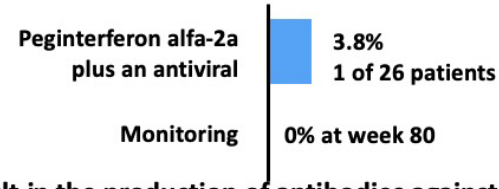
Result in the disappearance of virus particles called HBsAg from the bloodstream?



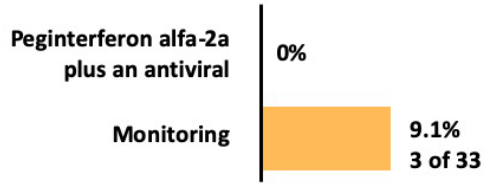
Result in the disappearance of virus particles called HBeAg from the bloodstream?



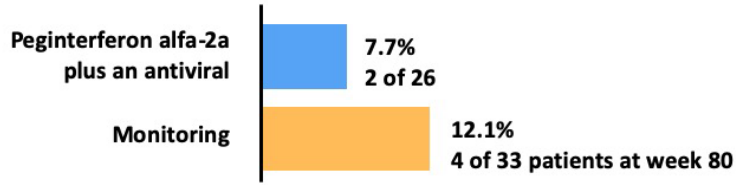
Result in the production of antibodies against HBsAg?



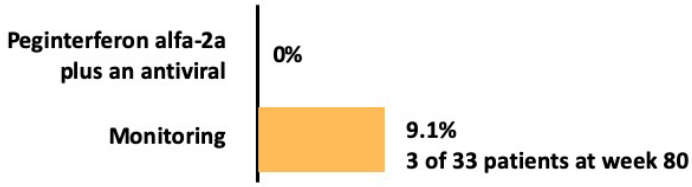
Result in the production of antibodies against HBeAg?



Decrease the amount of virus particles called HBV DNA in the bloodstream?



Result in the production of antibodies against HBeAg and decrease the amount of HBV DNA in the bloodstream?

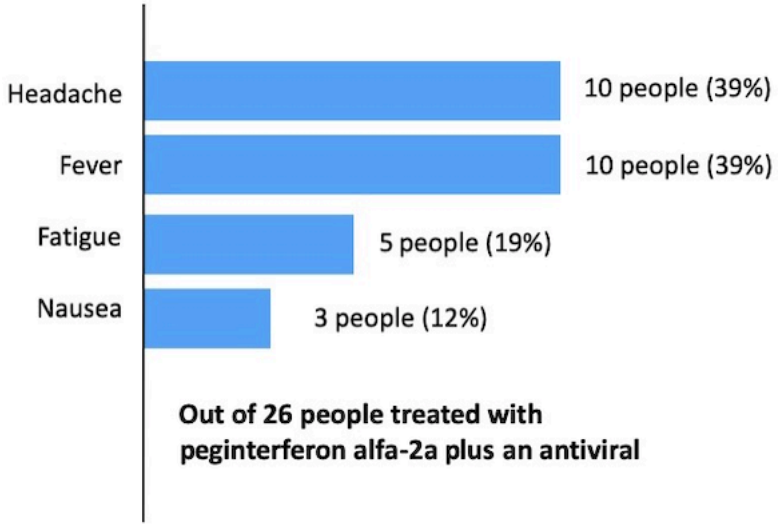


5. What were the side effects of treatment?

Side effects

During this study, almost everyone who received treatment with peginterferon alfa-2a plus an antiviral medicine (92%) had at least 1 side effect that was not considered serious.

The most common treatment-related side effects are shown in the following bar chart – these are the four most common side effects in people treated with peginterferon alfa-2a plus an antiviral.



6. How has this study helped clinical research?

The information presented here is from a single study of 59 children and adolescents with immune-tolerant chronic hepatitis B. People living with immune-tolerant chronic hepatitis B are generally not treated with medicine. Instead, their doctors check them frequently and start medicines when their immune system starts fighting the infection.

The results in this study helped clinical researchers understand that treatment with peginterferon alfa-2a plus either lamivudine or entecavir is not helpful at this stage of the disease.

Treatment with peginterferon alfa-2a plus either lamivudine or entecavir was no better than checking people frequently. Most people in the study also had side effects.

Two other studies in people with immune-tolerant chronic hepatitis B have also found that these medicines do not cause the immune system to fight the infection (listed at the end of this document).

This means that different medicines are needed to treat people with immune-tolerant chronic hepatitis B.

7. Are there plans for other studies?

Due to the lack of effect of peginterferon alfa-2a plus an antiviral in this study in children, and the lack of effect of peginterferon alfa-2a plus entecavir in two other studies in people with the same condition (one in children and one in adults), no further studies of this combination are planned. This study has helped researchers understand that new treatment strategies are required to change the course of immune-tolerant chronic hepatitis B. Future medicines will be tested in people with this type of chronic hepatitis B.

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/NCT02263079
- https://forpatients.roche.com/en/trials/infectious-diseases/hbv/a-study-of-pegylated-interferon-alfa-2a-in-combination-with-lami.html

The publication of this study is:

Mieli-Vergani G, Bansal S, Daniel JF, et al. Peginterferon Alfa-2a (40KD) Plus Lamivudine or Entecavir in Children with Immune-tolerant Chronic Hepatitis B. Journal of Pediatric Gastroenterology and Nutrition. 2021; published ahead of print (https://journals.lww.com/jpgn/Abstract/9000/Peginterferon_Alfa_2a__40KD__Plus_Lamivudine_or.95717.aspx). doi: 10.1097/MPG.0000000000003118.

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/en/trials/infectious-diseases/hbv/a-study-of-pegylated-interferon-alfa-2a-in-combination-with-lami.html
- Contact a representative at your local F. Hoffmann-La Roche office.

If you or your child took part in this study and you have any questions about the results:

- Speak to the study doctor or staff at the study hospital or clinic.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd, which has its headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “A study of pegylated interferon alfa-2a plus lamivudine or entecavir compared with untreated control group in children with hepatitis B envelope antigen (HBeAg)-positive chronic hepatitis B (CHB) in the immune-tolerant phase”

- The protocol number for this study is: NV25361
- The ClinicalTrials.gov identifier for this study is: NCT02263079.
- The EudraCT number for this study is: 2006-000977-31.
- Other important studies in persons with immune-tolerant chronic hepatitis B:

Rosenthal P, Ling SC, Belle SH, et al. Combination of entecavir/peginterferon alfa-2a in children with hepatitis B e antigen-positive immune-tolerant chronic hepatitis B virus infection. Hepatology. 2019;69(6):2326-2337.

Feld JJ, Terrault NA, Lin HS, et al. Entecavir and peginterferon alfa-2a in adults with hepatitis B e antigen-positive immune-tolerant chronic hepatitis B virus infection. Hepatology. 2019;69(6):2338-2348.