Summary of Clinical Trial Results

A study to look at whether different study medicine combinations worked and how safe they were when given to people with long-term hepatitis B virus infection

See the end of the summary for the full title of the study.

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) called the PIRANGA Hepatitis B study.

This summary is written for:

- Members of the public and
- People who took part in the study.

This summary is based on information known at the time of writing.

The PIRANGA study started in July 2020 and is planned to end in January 2025.

This summary presents results that were reported in July 2024. This includes complete results for the Combo 2, 3, 4 and 6 groups and results for people who had finished treatment in the Control group.

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 part of the PIRANGA 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

Glossary

- HBV= hepatitis B virus
- NUC = nucleoside or nucleotide analogues

Thank you to the people who took part in this study

The people who took part in this part of the PIRANGA study (known as 'participants') have helped researchers to answer important questions about hepatitis B virus (HBV) infections that are long-term and ongoing and the medicines studied – xalnesiran (siRNA), ruzotolimod (TLR7), pegylated interferon-alpha (PEG-IFNα) – and standard-of-care medicines: entecavir (ETV), tenofovir disoproxil fumarate (TDF) and alafenamide disoproxil fumarate (TAF).

Key information about this study

- The PIRANGA study looked at hepatitis B virus (HBV) and levels of a protein on the surface of HBV, called a 'surface antigen'. The PIRANGA study tested how well different combinations of existing medicines and study medicines lowered levels of HBV and its surface antigen so that they could not be detected on tests. Researchers also wanted to see how safe the medicines were
- This summary presents results reported in July 2024. This includes complete results for the Combo 2, 3, 4 and 6 groups and results for participants who completed the study in the Control group
- In this part of the study, participants continued their existing standard-of-care treatment, which were nucleoside or nucleotide analogues, called 'NUCs' (ETV, TAF or TDF). Some participants were also given study medicines, as follows:
    - **Control group:** NUC
    - **Combo 2 group:** NUC and the study medicine siRNA 100mg
    - **Combo 3 group:** NUC and the study medicine siRNA 200mg
    - **Combo 4 group:** NUC and the study medicines siRNA 200mg and PEG-IFNα
    - **Combo 6 group:** NUC and the study medicines siRNA 200mg and TLR7
- It was decided by chance which group each participant would join
- This study included 160 people in 9 countries and 159 were included in the analyses
- Researchers found that more people had undetectable HBV surface antigen in their blood when taking siRNA 200mg and PEG-IFNα (Combo 4) or siRNA 200mg and TLR7 (Combo 6) compared with people taking NUC alone (Control).
- No new safety concerns were found:
    - 1 out of 159 people (less than 1%) had a serious unwanted effect due to PEG-IFNa compared with 0 people taking NUC alone
- At the time of writing this summary, the PIRANGA study is still happening. It is planned to end in January 2025

1. General information about this study

Why was this study done?

Hepatitis B is a liver infection caused by the hepatitis B virus (HBV). HBV is a virus that causes the liver to swell up and become inflamed. Some people with HBV are sick for only a few weeks (known as 'acute' infection), but for others, the disease progresses to a serious lifelong illness known as chronic HBV infection. Chronic means it is continuous for a long period of time. Long-term HBV infection increases a person's risk of developing liver cancer or cirrhosis. Cirrhosis is a condition that permanently scars the liver and prevents it from working properly.

HBV puts the instructions for making copies of itself (called 'DNA') in liver cells. This causes liver cells to make more HBV, including a part of the virus called 'surface antigen'. An antigen is a substance, like a piece of a virus or pollen, that the body recognises as foreign, which triggers a response of the immune system. The immune system is the body's natural defence, which protects the body from foreign or harmful substances such as bacteria and viruses. In a working immune system, the body produces specific proteins in the blood called 'antibodies' that can stick to HBV (known as 'seroconversion'). Having HBV antibodies is an indicator of immune control of HBV infection.

In long-term HBV infections, completely removing all HBV DNA – known as a 'disease cure' – is currently not possible. However, when HBV DNA and HBV surface antigen is lowered so that it can't be detected in the blood, it's called a 'functional cure'. Lowering the amount of HBV surface antigen until it cannot be detected on tests, may stop the disease getting worse.

Standard-of-care medicines are the accepted standard treatment usually given to people with a disease. Medicines that help fight viruses are called 'antivirals'. There are two types of antiviral standard-of-care medicines for long-term HBV infection:

- Nucleoside or nucleotide analogues, called 'NUCs'
- Pegylated interferons (long-acting interferons), called 'PEG-IFNα'

These medicines can reduce a person's level of HBV and the chance of liver problems, but:

- NUC treatments need to be taken long term, sometimes for a person's whole life, and are not effective for everyone
- PEG-IFNα need to be taken for up to a year and can cause unwanted effects
- NUC and PEG-IFNα treatment result in a functional cure in only a small number of people with long-term HBV infection (about 1 in every 33 people [3%])

More effective medicines are needed to reduce the level of virus and cure people of long-term HBV infections.

The PIRANGA study is looking at how well standard-of-care medicines alone lower HBV surface antigen levels in the body compared with when they are taken with different antiviral medicine combinations. Researchers are also looking at how safe the medicine combinations are.

What were the study medicines in this part of study medicines?

The PIRANGA study is still ongoing. This summary includes only the results for the Combo 2, 3, 4 and 6 groups from the PIRANGA study and participants who completed the study in the Control group.

Everyone in the PIRANGA study continued their existing standard-of-care medicines, which were NUCs (ETV, TAF, or TDF).

Some groups were also given study medicines to see if combinations of medicines worked better than standard-of-care medicines alone. Researchers compared NUC standard-of-care treatment on its own or with the medicines being studied so they could show which benefits or unwanted effects are actually caused by the medicines.

'PEG-IFNα'

- Also known as 'pegylated interferon-alpha'. You say this as 'peg-uh-lay-ted in-ter-fear-on al-fuh'
- PEG-IFNα is an anti-viral medicine and works by helping the immune system to fight the HBV. It is approved for treating chronic HBV

'TLR7'

- Also known as 'ruzotolimod'. You say this as 'ru–ZOH–toll–i–mod'
- TLR7 works by helping the immune system to fight the HBV
- This may mean TLR7 is able to help the immune system fight the HBV

'siRNA'

- Also known as 'xalnesiran'. You say this as 'zall–NI–sih–ran'
- siRNA works by stopping new HBV from being made
- This may mean that siRNA could lower the amount of HBV in the body

What did researchers want to find out?

- Researchers are doing the PIRANGA study to compare NUC standard-of-care medicines with or without different study medicines – to see how well different study medicine combinations work (see section 4 'What were the results of the groups?')
- They also wanted to find out how safe the study medicine combinations were – by checking how many people had unwanted effects and seeing how serious they were when taking each of the medicines during the study (see section 5 'What were the unwanted effects experienced in the groups?')

The main question that researchers wanted to answer was:

1. How many participants did not have any HBV surface antigen detected in their blood 6 months after their last dose of study medicines?

Another question that researchers wanted to answer was:

2. How many participants showed signs that their immune system could control the HBV virus by making antibodies (seroconversion)?

What kind of study was this?

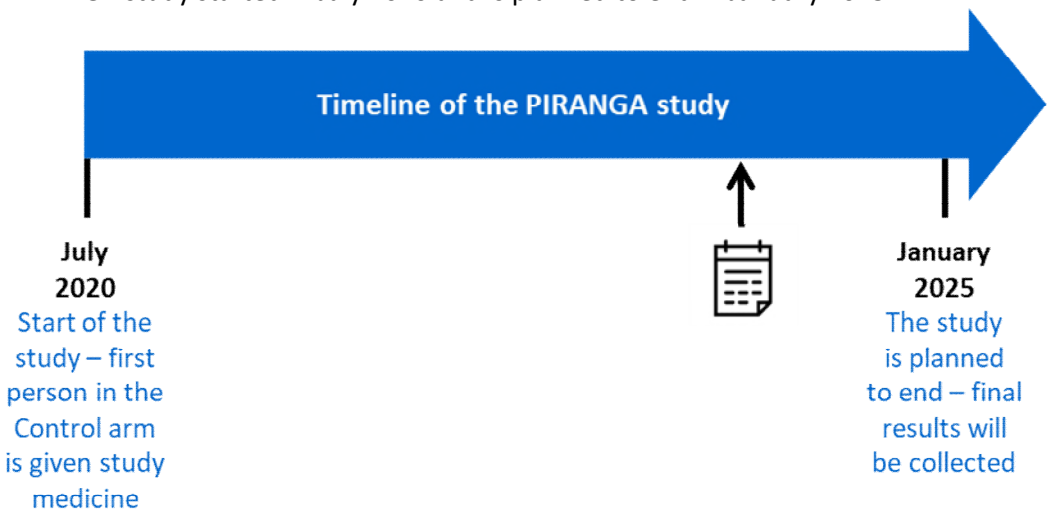
The PIRANGA study is a 'Phase 2' study. This means that the safety of TLR7 and siRNA had been tested in a number of people with and without long-term HBV infections before this study. In this part of the study, people with long-term HBV infections took NUC standard-of-care treatment on its own or with siRNA alone, or siRNA and PEG-IFNα, or siRNA and TLR7. This was to find out if treatment with NUC and the study medicines was better than NUC alone at lowering HBV and its surface antigen to undetectable levels. They also wanted to find out how safe the study medicine combinations were.

The PIRANGA study is 'randomised'. This means that it was decided by chance which of the medicines people in the study would have. Randomly choosing which medicine people take makes it more likely that the types of people in each group (for example, age, race) will be a similar mix. Apart from the exact medicines being tested, all other aspects of care were the same between groups.

The PIRANGA study is also 'open-label'. This means everyone involved, including the person in the study and the study doctor, knew the study medicines the person was being given.

When and where did the study take place?

The PIRANGA study started in July 2020 and is planned to end in January 2025.



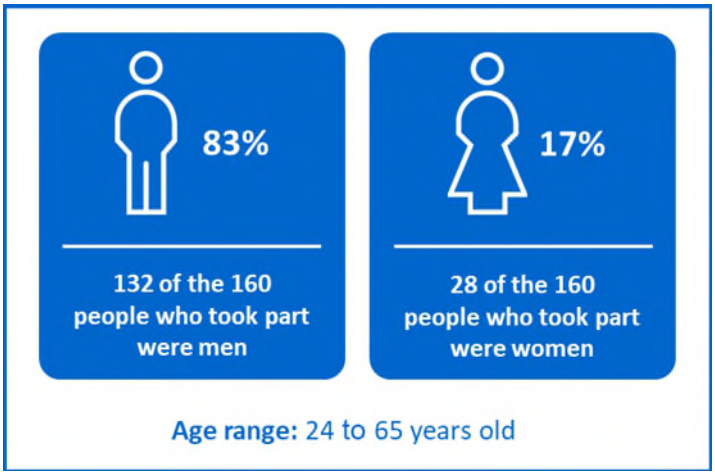
The symbol on the timeline ( ) shows when information from the Combo 2, 3, 4 and 6 groups were reported – in July 2024

This part of the study took place at 22 study centres – across 9 countries. The countries were: Chile, China, France, Hong Kong, New Zealand, Republic of Korea, Spain, Taiwan and Thailand.

2. Who took part in this study?

In this study, 160 people with long-term HBV infections who had their virus levels controlled with NUC therapy, took part in the Combo 2, 3, 4, 6 or Control groups and 159 were included in this analysis.

People who took part were between 24 and 65 years of age. 132 of the 160 people (83%) were male and 28 of the 160 people (17%) were female.



People could take part in the study if they:

- Were aged 18 to 65 years old
- Had a HBV infection for at least 6 months that was controlled by NUC medicines
- Had been treated with NUC medicines for at least 12 months
- Had not changed to a different NUC medicine within 3 months of joining the study

People could not take part in the study if they:

- Had certain other medical conditions, such as scarring of the liver, heart disease or certain infections
- Had thyroid disease that was not controlled with medicines
- Had a history of or were likely to have liver cancer
- Were being or had recently been treated with certain other treatments, such as medicines for killing cancer cells (chemotherapy), reducing inflammation (corticosteroids) or medicines that affect the immune system
- Had been treated with another clinical study drug for HBV infection within 6 months of taking part in the study
- Were pregnant, breastfeeding or planned on becoming pregnant during the study or within 6 months after the last dose of study medicine
- Did not meet the criteria to join one of the groups

3. What happened during the study?

During the PIRANGA study, people were selected by chance to go into 1 of up to 9 groups – including 1 Control group and 8 study medicine groups. The treatments were selected at random – by a computer. Selection also depended on which groups were open to new participants at the time they took part in the study and if participants met the criteria to join certain groups.

Only details of the Combo 2, 3, 4, 6 and Control groups are included in this summary.

The treatments given to Combo 2, 3, 4 and 6 groups were:

- **NUC** (existing medicine) – continued to be taken as a pill, to be swallowed once a day until certain criteria were met or until the decision was made to stop treatment
- AND **siRNA** (the medicine being studied) – given as an injection under the skin once a month for up to 1 year (48 weeks) or until the decision was made to stop treatment

AND

Combo 4 group only

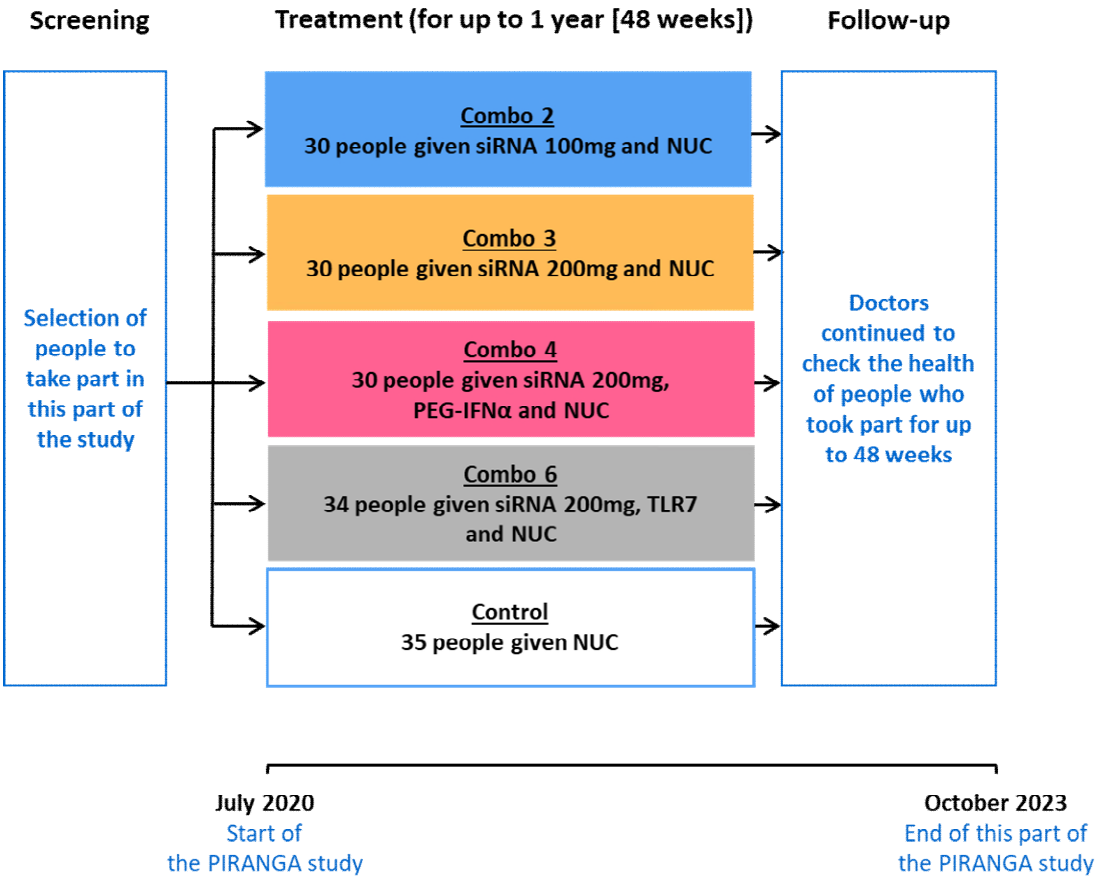
- **PEG-IFNα** (existing medicine) – given as an injection under the skin once a week for up to 1 year (48 weeks) or until the decision was made to stop treatment

Combo 6 group only

- **TLR7** (the medicine being studied) – given as a pill to be swallowed once every other day or weekly during Weeks 13 to 24 and Weeks 37 to 48 only or until the decision was made to stop treatment

After people finished taking their medicine for this part of the study, they were asked to go back to their study centre for more visits – to check their overall health.

The study flow chart shows all stages for the Combo 2, 3, 4 and 6 groups and the Control group.



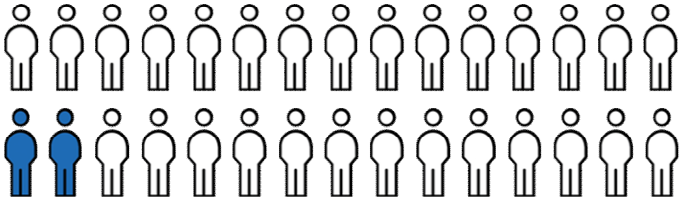
4. What were the results of the study?

Question 1: How many participants did not have any HBV surface antigen detected in their blood 6 months after their last dose of study medicines?

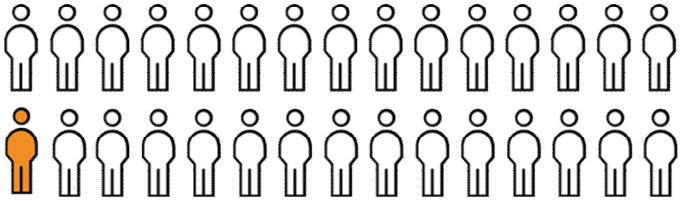
Researchers wanted to see if the study medicines could lower the amount of HBV and its surface antigen to levels that could not be detected in the blood tests 6 months after finishing treatment. This could help prevent the disease getting worse.

6 months after finishing treatment, the number of people with undetectable HBV surface antigen in their blood were.:

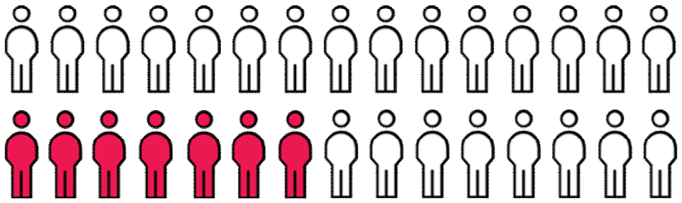
Combo 2 **2 in every 30 people (7%)** taking siRNA 100mg and NUC had undetectable HBV surface antigen levels



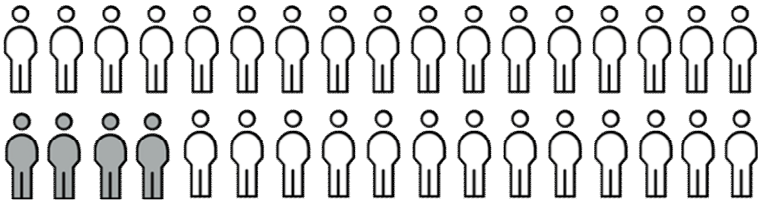
Combo 3 **1 out of 30 people (3%)** taking siRNA 200mg and NUC had undetectable HBV surface antigen levels



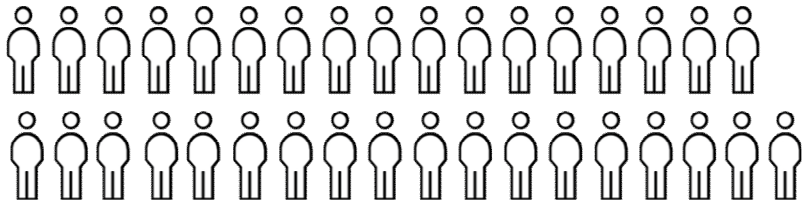
Combo 4 **7 out of 30 people (23%)** taking siRNA 200 mg and PEG-IFNα and NUC had undetectable HBV surface antigen levels



Combo 6 **4 out of 34 people (12%)** taking siRNA 200 mg and TLR7 and NUC had undetectable HBV surface antigen levels



Control **0 out of 35 people (0%)** taking NUC only had undetectable HBV surface antigen levels



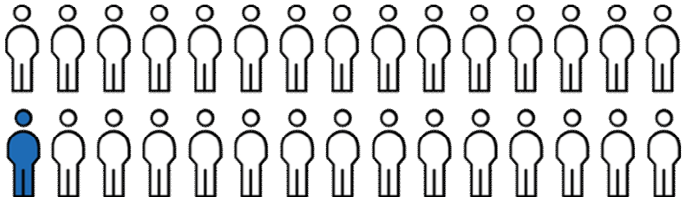
- More people in the Combo 4 and 6 groups (siRNA and PEG-IFNα and NUC, siRNA and TLR7 and NUC) had undetectable HBV surface antigen in their blood 6 months after finishing treatment compared with the Control group taking NUC only
- The Combo 4 group (siRNA and PEG-IFNα and NUC) had the most people with undetectable HBV surface antigen in their blood 6 months after finishing treatment

Question 2: How many participants showed signs that their immune system could control the HBV by making antibodies (seroconversion)?

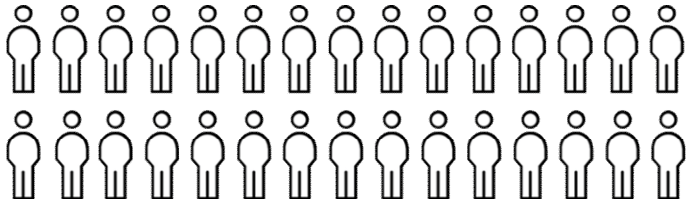
Researchers wanted to see if the study medicines increased the number of antibodies in the blood tests 6 months after finishing treatment, as this would show HBV is controlled by the body's immune system.

6 months after finishing treatment, the number of people with HBV antibodies were:

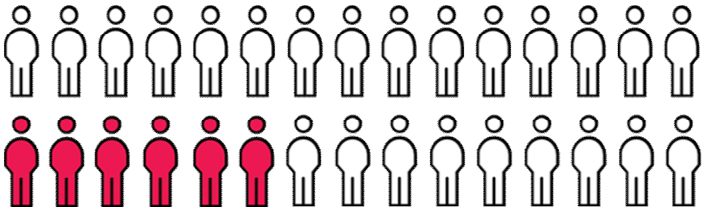
Combo 2 **1 in every 30 people (3%)** taking siRNA 100mg and NUC had HBV antibodies in their blood



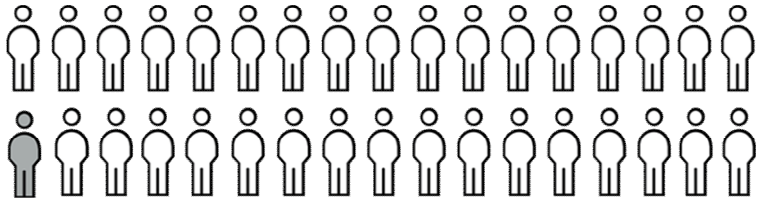
Combo 3 **0 out of 30 people (0%)** taking siRNA 200mg and NUC had HBV antibodies in their blood



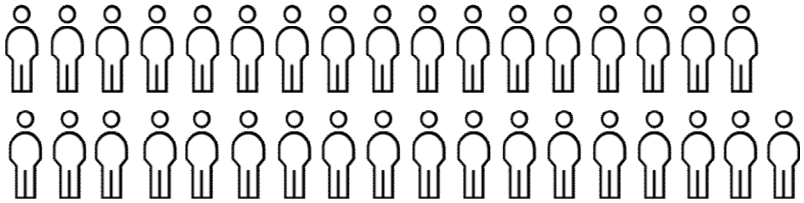
Combo 4 **6 out of 30 people (20%)** taking siRNA 200 mg and PEG-IFNα and NUC had HBV antibodies in their blood



Combo 6 **1 out of 34 people (3%)** taking siRNA 200 mg and TLR7 and NUC had HBV antibodies in their blood



Control **0 out of 35 people (0%)** taking NUC only had HBV antibodies in their blood



- The Combo 4 group (siRNA and PEG-IFNα and NUC) had the highest number of people with the most antibodies in their blood 6 months after completing treatment

This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see section 8).

5. What were the unwanted effects?

Unwanted effects are medical problems (such as feeling dizzy) that happen during the study.

- They are described in this summary because the study doctor believes the unwanted effects were related to the treatments in the study.
- Not all of the people in this study had all of the unwanted effects.
- Unwanted effects may be mild to very serious any can be different from person to person.
- It is important to be aware that the unwanted effects reported here are from this single study. Therefore, the unwanted effects shown here may be different from those seen in other studies, or those that appear on the medicine leaflet(s).
- Serious and common unwanted effects are listed in the following sections.

Serious unwanted effects

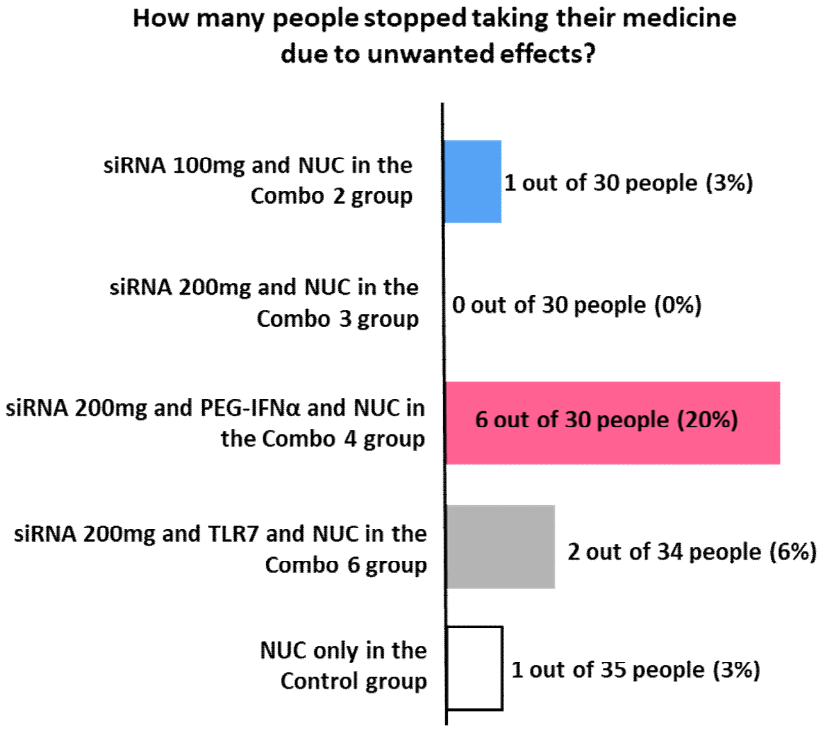
An unwanted effect is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.

During this part of the study, 1 out of 159 people (less than 1%) had a serious unwanted effect related to the study treatment of PEG-IFNα:

- This person was taking siRNA 200mg and PEG-IFNα and NUC in Combo 4 group, and had a sudden episode of intense fear or anxiety (a panic reaction)

No one in any of the groups died due to unwanted effects that may have been related to any of the study medicines.

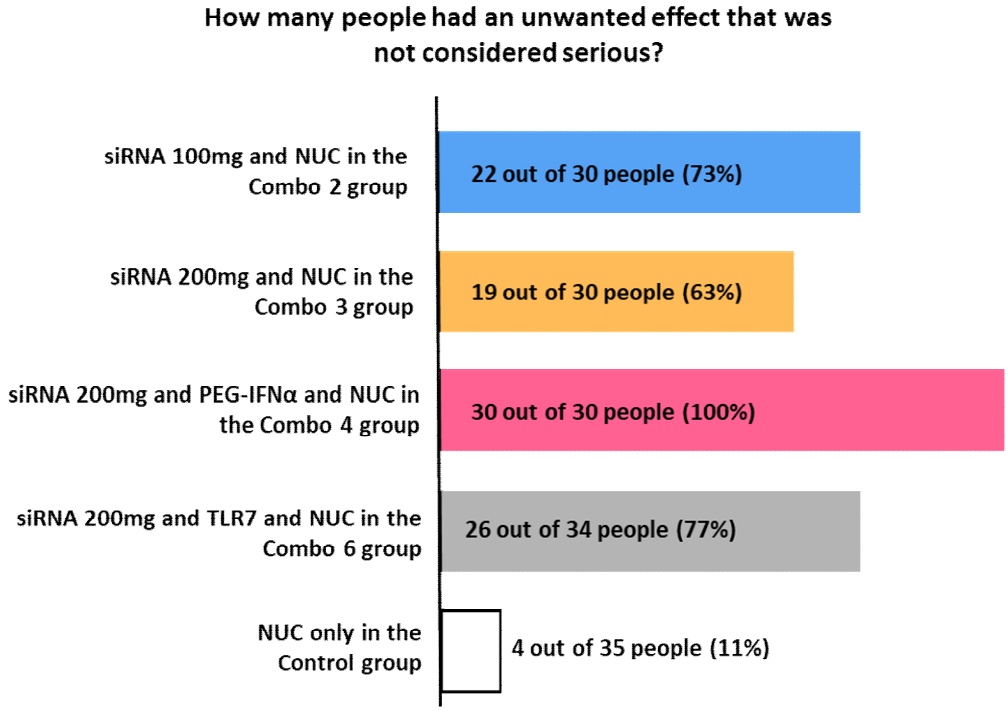
During this part of the study, some people stopped taking their medicine due to unwanted effects:



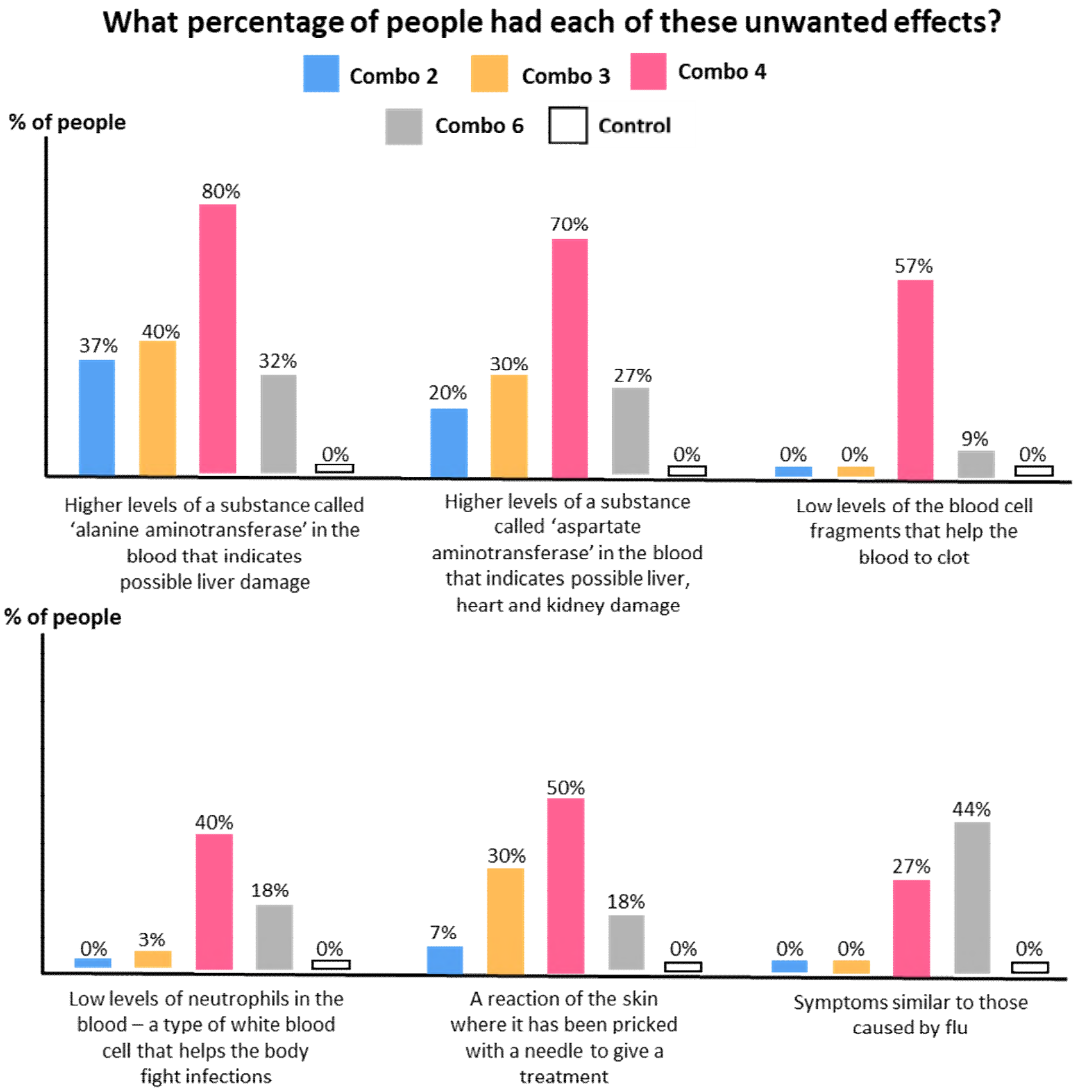
Most common unwanted effects

Overall, all 5 treatment combinations were well tolerated. The unwanted effects of each of the combined treatments (Combo 2, Combo 3, Combo 4, and Combo 6) were as expected based on the known risks of the individual treatments. No new safety concerns were found.

During this part of the study, around 8 of every 10 people (78%) overall had an unwanted effect that was not considered serious.



The most common unwanted effects are shown in the following picture – these are the 6 most common unwanted effects in this part of the study. Some people had more than one unwanted effect – this means that they are included in more than one part of the picture.



Other unwanted effects

You can find information about other unwanted effects (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

6. How has this study helped research?

The information presented here is from part of the PIRANGA study of people with a long-term HBV infection. These results are from the Combo 2, 3, 4 and 6 groups that were reported in July 2024. These results helped researchers learn more about HBV infections and the medicines studied – NUC, PEG-IFNα, TLR7 and siRNA.

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at siRNA or TLR7 are planned.

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/results/ NCT04225715
- https://forpatients.roche.com/en/trials/infectious-diseases/hbv/a-trial-to-evaluate-the-efficacy-and-safety-of-multiple-42976.html

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-trial-to-evaluate-the-efficacy-and-safety-of-multiple-42976.html
- Contact a representative at your local Roche office

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

- Speak with the study doctor or staff at the study hospital or clinic

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: 'A phase II, randomised, adaptive, open-label platform trial to evaluate efficacy and safety of multiple combination therapies in participants with chronic Hepatitis B'.

The study is known as 'PIRANGA'.

- The protocol number for this study is: WV41073.
- The ClinicalTrials.gov identifier for this study is: NCT04225715.
- The EudraCT number for this study is: 2019-002086-35.