Clinical trial results – layperson summary

A study to look at the safety and effectiveness of baloxavir marboxil in treating children with influenza aged between 1 and <12 years (miniSTONE-2)

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) – written for:

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

This summary is based on information known at the time of writing (September 2019). More information may now be known.

No single study can tell us everything about the risks and benefits of a medicine and the results from one study may be different from other studies with the same medicine.

Contents of the summary

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about influenza and baloxavir marboxil.

Key information about baloxavir marboxil and this study

- About baloxavir marboxil
  - Baloxavir marboxil is a treatment known as an 'antiviral', a type of drug that attacks a virus and treats viral infections
  - It was first approved in Japan in 2018 and since then has been approved in several countries to treat flu

- About this study:
  - This was the first global study carried out to confirm the safety of baloxavir marboxil in children with flu-like symptoms aged between 1 and <12 years, and to investigate its effectiveness in this population
  - Children who participated in this study were otherwise healthy with no major health issues
  - This study included 176 children
  - Children were given either baloxavir marboxil or oseltamivir (another antiviral approved for the treatment for flu)
  - Similar to previous studies, no major safety concerns were identified in children treated with baloxavir marboxil
  - The effectiveness of baloxavir marboxil in reducing the symptoms of flu was similar to that of oseltamivir
  - Baloxavir marboxil also reduced the length of time that patients release (or 'shed') infectious virus
  - There was no major impact on the benefits of baloxavir marboxil in patients with flu virus that developed mutations

1. General information about this study

Why was this study carried out?

Influenza, also known as flu, is a common, but potentially serious illness caused by infection with the flu virus. It mainly affects the lungs, and common symptoms include headaches, fevers, joint pain and feeling extremely tired.

In some cases, flu may cause severe complications leading to hospitalisations and even deaths. Each year, millions of people worldwide are hospitalised due to a complicated course of flu and up to 650,000 die of its consequences (WHO 2017).

Although many over the counter medications may help to reduce some flu symptoms, the only treatments that attack the flu virus directly are antivirals. These can be prescribed by a doctor or pharmacist.

Flu is very common and can be particularly dangerous in children, therefore new and improved 'antiviral' treatments for these patients are always needed. This study was carried out to see if baloxavir marboxil, an antiviral treatment that is proven in adults, could also be used to treat children with flu-like symptoms. Two small studies in Japan has shown good safety of baloxavir marboxil in children, however, this was the first global study in children.

World Health Organisation (WHO) Statements. 2017. Available at https://www.who.int/mediacentre/news/statements/2017/flu/en/ accessed September 2019

What was the study medicine?

In this trial, a medicine called baloxavir marboxil was compared with another medicine called oseltamivir.

- Baloxavir marboxil is an antiviral treatment that is already approved for adults and adolescents in some countries, such as the USA and Japan
- Baloxavir marboxil is approved for children who weigh more than 10 kg in Japan
- Oseltamivir is an antiviral treatment that is already approved for adults and children of all ages

What did researchers want to find out?

1. Researchers did this study to confirm that baloxavir marboxil was safe to give to children aged between 1 and <12 years old by looking at the side effects during the study (see section 4 "What were the results of the study?")
2. They also wanted to find out the effectiveness of baloxavir marboxil in children compared with oseltamivir, a treatment that is already approved to treat children and adults with flu

The main question that researchers wanted to answer was
What were the side effects of baloxavir marboxil in children aged between 1 and <12 years?

Other questions that researchers wanted to answer included
How effective is baloxavir marboxil in children aged between 1 and <12 years?
How does the body process a single dose of baloxavir marboxil?
How many participants had flu virus with mutations after treatment with baloxavir marboxil?

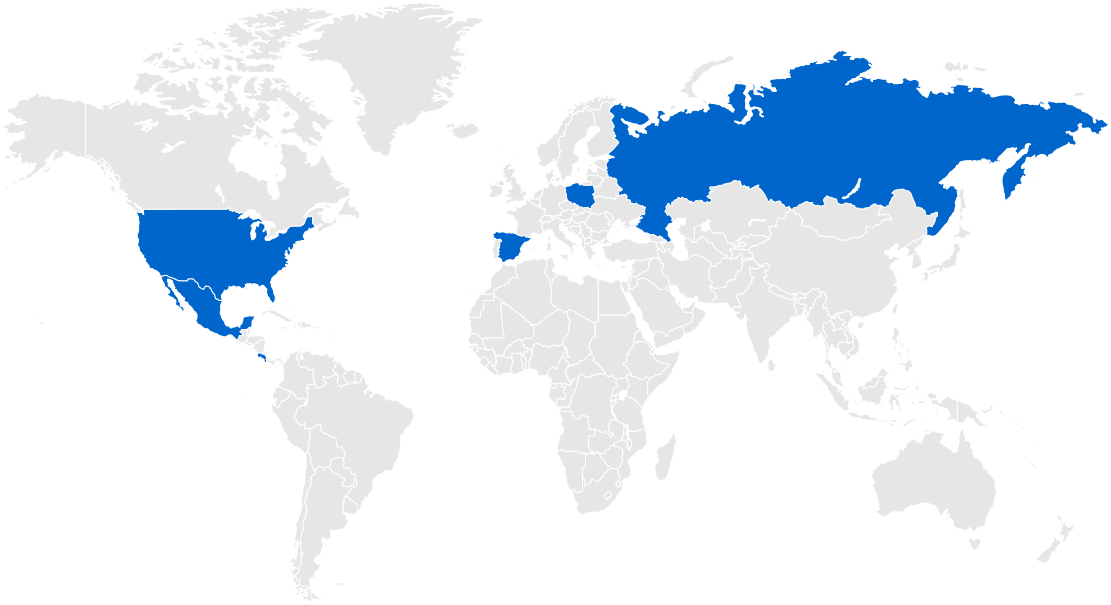
What kind of study was this?

This study was a 'phase 3, randomised, double-blind' study:

- A 'phase 3' study is a large-scale study to confirm and expand on the results of previous studies
- A 'randomised' study means that patients were split into treatment groups by chance (like flipping a coin)
- A 'double-blind' study means that no one involved in the study knew which group they were in, or what treatment they were receiving

When and where did the study take place?

This was a global study and took place across USA, Costa Rica, Mexico, Spain, Poland and Russia. It was carried out during the 2018/2019 northern-hemisphere influenza season. The following map shows the countries where this study took place.



2. Who took part in this study?

Children with flu-like symptoms who had a fever (temperature of 38°C or above) and a cough or other flu-like symptoms (such as congestion) for no longer than the last 48 hours could take part in the study.

Overall, 176 children aged between 1 and <12 years were enrolled in the study.

- Approximately one third of patients were aged between 1 and 5 years, and two thirds aged between 5 and <12 years
- The majority of patients in the study were of White race
- Approximately half of all patients had previously been vaccinated for influenza
- All children were healthy with no major medical conditions

3. What happened during the study?

During the study, patients were selected randomly to get one of two treatments. The groups in this study were not equal in size – for every two patients selected to receive baloxavir marboxil, one patient was selected to receive oseltamivir. This meant that twice as many patients received baloxavir marboxil than oseltamivir.

The diagram below shows which patients were enrolled to receive each treatment:

Enrolled to take part in the study

117 people in the baloxavir marboxil group

59 people in the oseltamivir group

- Patients in the baloxavir marboxil group received a single oral dose of baloxavir marboxil on Day 1 (based on body weight) and a placebo (a tablet with no active medicine) taken orally twice daily for 5 days
- Patients in the oseltamivir group received oseltamivir taken orally twice daily for 5 days and a single oral placebo taken on the Day 1

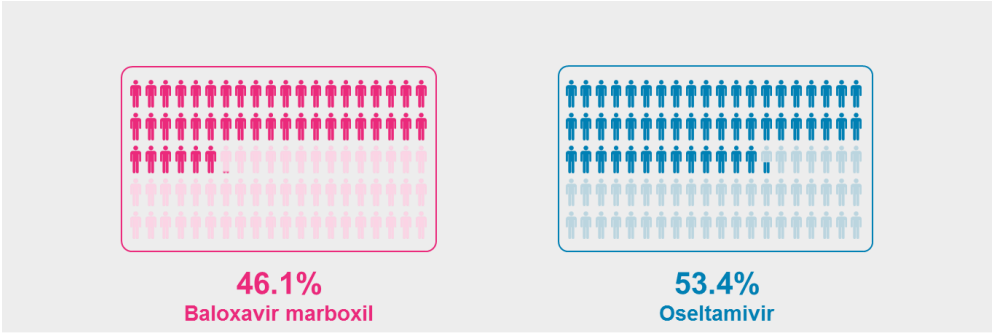
Parents or caregivers reported the severity of symptoms and as well as how they were feeling/behaving more generally. They also measured temperature throughout the study. Children were monitored during scheduled visits by study investigators:

- To track baloxavir marboxil in the body, blood samples were taken throughout the clinical trial and we measured the amount of baloxavir in the blood at different times after taking the drug
- To look at the effect of baloxavir marboxil on the flu virus, we also took swabs from inside the nose
- Any adverse (undesirable) events that the participants experienced during the trial were also recorded, and these could be due to the flu virus, baloxavir marboxil, oseltamivir or any other reason

4. What were the results of the study?

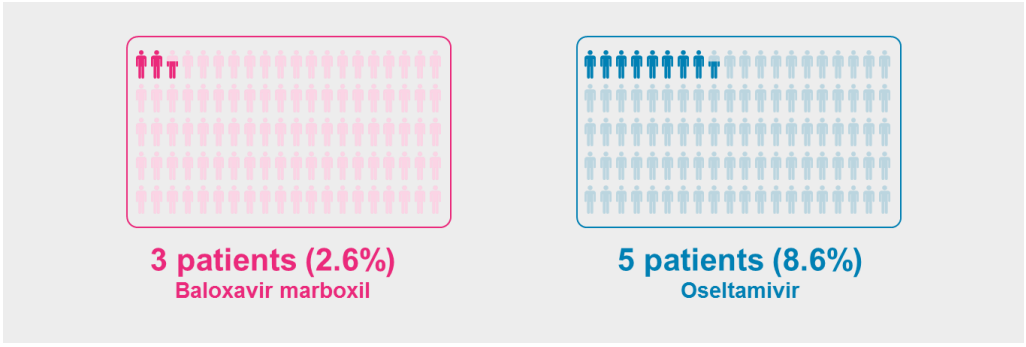
The main question: What were the side effects of baloxavir marboxil in children aged between 1 and <12 years?

Researchers first looked at the overall number of **all reported side effects** that patients experienced during the study, independently whether these were caused by the treatment or not. The figure below shows how many patients in each group had at least one such side effect. None of the side effects were serious. These results are similar to the results of previous studies with baloxavir marboxil in children.



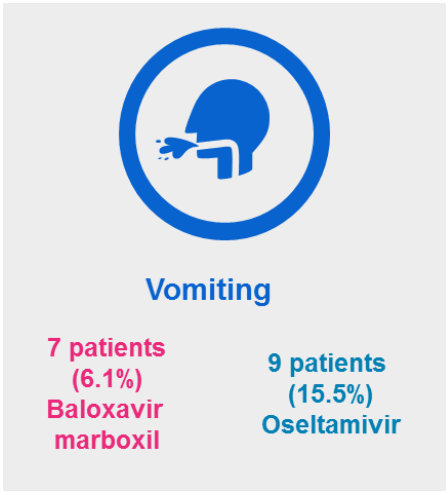
Then researchers looked at the number of patients who had at least one **side effect that doctors think was related to the treatments** being given (baloxavir marboxil or oseltamivir).

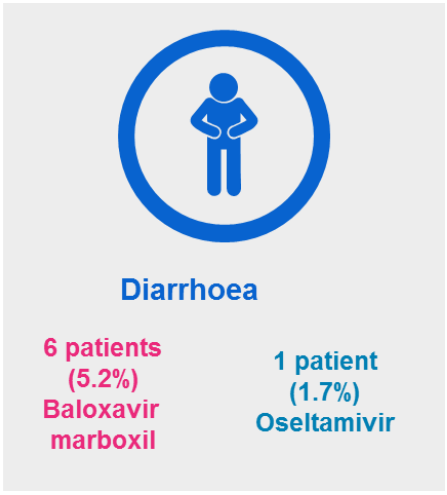
The figure below shows that the number of side effects that doctors believed were related to treatment was low for both groups:



What were the most common side effects?

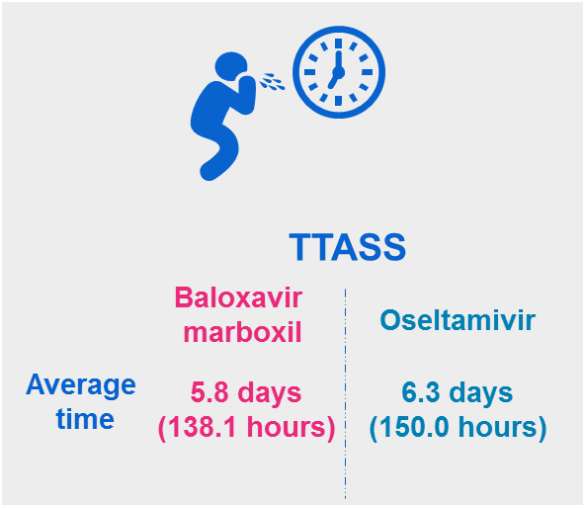
Researchers found that the most common side effects were vomiting and diarrhoea. Vomiting was more common in people who took oseltamivir, but diarrhoea was more common in people taking baloxavir marboxil.





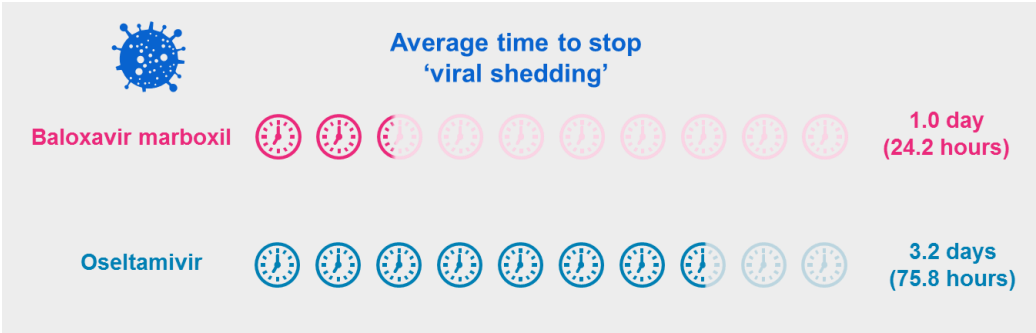
Other questions: How effective is baloxavir marboxil in children aged between 1 and <12 years?

Researchers also looked at how quickly patients' symptoms resolved and when they returned to normal health and activity. The average time was found to be similar for both treatments:



The number of patients who had complications due to influenza or required antibiotics for other infections caused by bacteria was similar in both groups.

Researchers also looked at something called 'viral shedding' (i.e. live, infectious virus released from a patient) and when this stopped after a dose of baloxavir marboxil. This study found that treatment with baloxavir marboxil markedly reduced the amount of time that patients were releasing infectious virus compared with oseltamivir:



How does the body process a single dose of baloxavir marboxil?

Baloxavir marboxil is converted to baloxavir (the active form of the drug) by the body. The amount (or 'concentration') of baloxavir that is in the blood, and the length of time it remains in the body, was found to be very similar in children when compared to adult patients.

How many participants had flu virus with mutations after treatment with baloxavir marboxil?

Sometimes, flu viruses can develop small changes in their genetic material known as 'mutations' during the course of treatment. This can mean that the treatment can become less effective. None of the participants had flu virus with these types of mutations before starting treatment with baloxavir marboxil. However, over the course of the study 11 patients developed mutations after receiving treatment with baloxavir marboxil. Despite this, there was no major impact on the effectiveness of baloxavir marboxil in treating symptoms in this group of patients, where results were similar to those taking oseltamivir.

5. How has this study helped research?

These results helped researchers learn more about the safety and effectiveness of baloxavir marboxil in children.

Key findings from this study:

- No major safety concerns were identified in children treated with baloxavir marboxil
- The effectiveness of baloxavir marboxil in reducing the symptoms of flu was similar to that of oseltamivir (an approved treatment already used to treat children with flu)
- Baloxavir marboxil also markedly reduced the time when patients shed infectious virus
- There was no major impact on the benefits of baloxavir marboxil in patients with flu virus that developed mutations

No single study can tell us everything about the risks and benefits of a medicine. It takes many 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

6. Are there plans for other studies?

Baloxavir marboxil is being studied in many different patients. The following studies are ongoing:

- miniSTONE-1 is looking at baloxavir marboxil in infants younger than 1 year old
- T0835 (a Japanese study) is looking at a different doses of baloxavir marboxil in children
- Flagstone is looking at baloxavir marboxil in hospitalized flu patients aged 12 and above
- CENTERSTONE is looking at the effect of baloxavir marboxil in preventing transmission of influenza in patients aged between 12 and less than 64 years

7. 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/ NCT03629184
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002169-21/results

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/influenza/study-to-assess-the-safety--pharmacokinetics--and-effic-62594.html

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 Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients 1 to <12 Years of Age With Influenza-Like Symptoms.

The study is also known as 'miniSTONE-2'.

- The protocol number for this study is: CP40563.
- The ClinicalTrials.gov identifier for this study is: NCT03629184.
- The EudraCT number for this study is: 2018-002169-21