A study to look at the safety and effectiveness of baloxavir marboxil, in addition to standard treatment, in severely ill, hospitalised people with influenza (FLAGSTONE)

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:

- people who took part in the study and
- members of the public

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

The study started in January 2019 and finished in March 2020. This summary was written after the study had ended.

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

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 (also known as flu) and baloxavir marboxil (baloxavir).

Key information about this study

- About baloxavir:
    - Baloxavir is a treatment that is known as an 'antiviral', a type of drug that helps to stop viruses from reproducing and treats viral infections. Baloxavir is an antiviral drug specific for flu viruses. It was first approved as a treatment for flu in 2018 (in Japan and the US) and since then has been approved in many other countries
- About this study:
    - This was a global study carried out to assess the effectiveness of baloxavir in hospitalised people with severe flu aged 12 and over
    - This study included 366 people who had been hospitalised with severe flu
    - All people received the standard antiviral treatment that they would have usually received in the hospital. Some people also received baloxavir
    - Adding baloxavir to standard antiviral treatment for people hospitalised with flu did not help people's symptoms to improve any quicker than the current standard treatment
    - No new safety concerns were found

1. General information about this study

Why was this study done?

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 people die of its consequences (WHO 2017).

Antivirals are treatments that target the flu virus directly, and can be prescribed by a doctor or pharmacist when someone becomes ill with flu. However, antivirals have not been proven in clinical trials to help people hospitalised with severe flu.

This study was carried out to see if baloxavir, an antiviral treatment that is already approved for people with flu who have not been hospitalised, can be used together with the standard treatment for severe flu in hospitals to improve time to recovery.

What was the study medicine?

A medicine called baloxavir was the focus of this study. Baloxavir is an antiviral treatment that has already been approved in countries like the USA and Japan for adults and adolescents who have not been hospitalised with flu.

All people in this trial received the standard antiviral treatment that they would be given in the hospital for severe flu. This means that all patients received either oseltamivir, zanamivir or peramivir.

As well as one of these drugs, people on the trial also received either the study medicine baloxavir or a placebo. The placebo was a tablet that looked the same as baloxavir but did not contain any real medicine. This means it had no medicine-related effect on the body. The two groups of people receiving either baloxavir or placebo (plus standard antiviral treatment) are known as the treatment groups.

What did researchers want to find out?

- Researchers did this study to compare baloxavir with a placebo, when used together with the standard antiviral treatment for people hospitalised with flu, to see whether adding baloxavir improved people's recovery and allowed them to leave hospital quicker (see section 4 "What were the results of the study?")
- They also wanted to find out how safe baloxavir was in people hospitalised with flu, by checking how many people had side effects and seeing how serious they were

The main question that researchers wanted to answer was:
Does adding baloxavir to the standard antiviral treatment for severe flu help people hospitalised with flu to get better quicker?

Other questions that researchers wanted to answer included:

1. How effective is baloxavir in treating people aged 12 or over, who have been hospitalised with flu?
2. What were the side effects of baloxavir in people hospitalised with flu?
3. Does baloxavir reduce the amount of virus being produced in the bodies of people hospitalised with flu, which can go on to infect other people?

What kind of study was this?

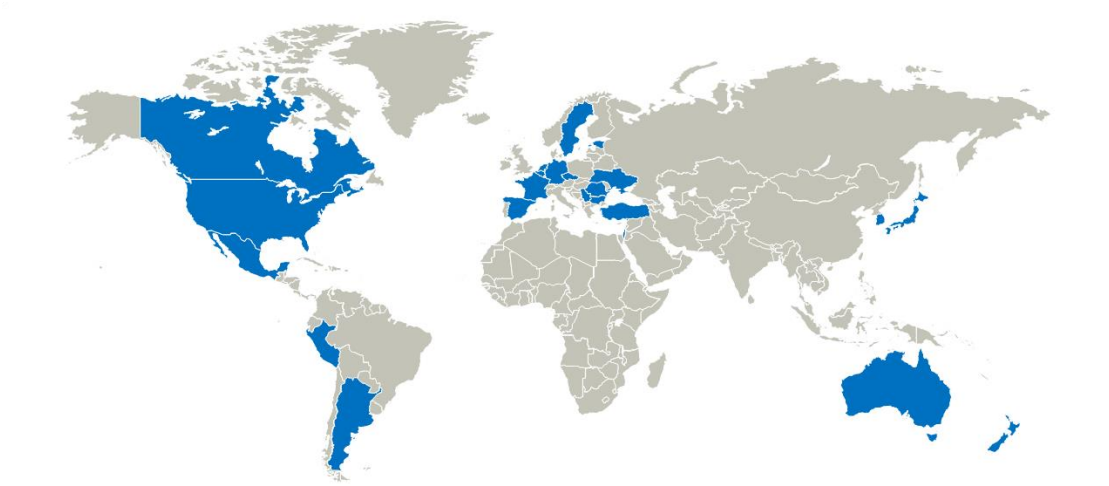
This study was a 'phase 3, randomised, double-blind' study

- A 'phase 3' study is a large-scale study to confirm and expand on the results of previous studies done with the study drug and different types of people with flu
- A 'randomised' study means that people were split into treatment groups by chance (like flipping a coin to decide which group they went into)
- A 'double-blind' study means that no one involved in the study knew which group they were in, or what treatment they were receiving; not the person receiving treatment, the doctor giving it, or Roche (the study sponsors)

When and where did the study take place?

The study started in January 2019 and finished in March 2020. This summary was written after the study had ended.

The study took place at 124 study centres, across 25 countries worldwide: USA, Argentina, Australia, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Hong Kong, Israel, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Peru, Romania, Serbia, Singapore, Spain, Sweden, Turkey, Ukraine



2. Who took part in this study?

In this study, 366 people who had been hospitalised with severe flu took part.

People who took part in the study were between 12 and 96 years of age.

People could take part in the study if:

- They were aged 12 years or over
- They were in hospital with flu because they needed breathing support, or because their flu had a complication (such as pneumonia) that meant that they needed to be in a hospital
- Their flu symptoms had been present for less than 96 hours
- They scored 4 or more on the NEWS2 scale that is used by hospitals to identify when a patient is seriously ill

People could not take part in the study if:

- They had already received equal to or more than 48 hours of antiviral treatment for their flu
- They weighed less than 40 kg
- They were expected to die or be discharged from hospital within the next 48 hours

3. What happened during the study?

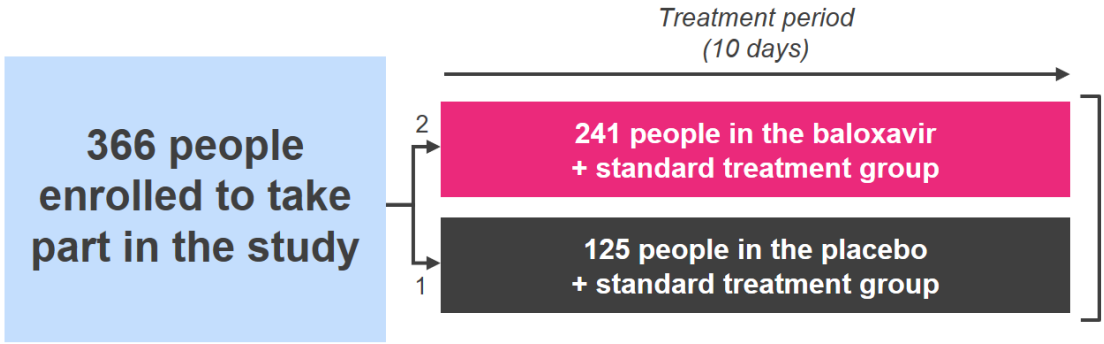
For each person on the study, the treatment group they were going to be in was decided at random by a computer.

The treatment groups were:

- **Baloxavir (the medicine being studied)** plus standard treatment for severe flu (one of oseltamivir, zanamivir or peramivir). Baloxavir was taken on days 1 and 4 (some people received another dose at day 7). The standard treatment was taken according to hospital guidelines
- **Placebo (a tablet/suspension with no active medicine)** plus standard treatment for severe flu (one of oseltamivir, zanamivir or peramivir). The placebo tablet/suspension was taken on days 1 and 4 (some people received another dose at day 7). The standard treatment was taken according to hospital guidelines

The groups in this study were not equal in size – for every two people selected to receive baloxavir plus standard treatment, one person was selected to receive placebo plus standard treatment. This meant that twice as many people received baloxavir than placebo. The 2:1 ratio helped to reduce the total number of people needed in the study to answer the research questions.

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



People in the study took the treatments for 10 days. When the study finished, the people who took part were asked to go back to their study centre for more visits to check their overall health. Look below to see more information about what happened in the study.

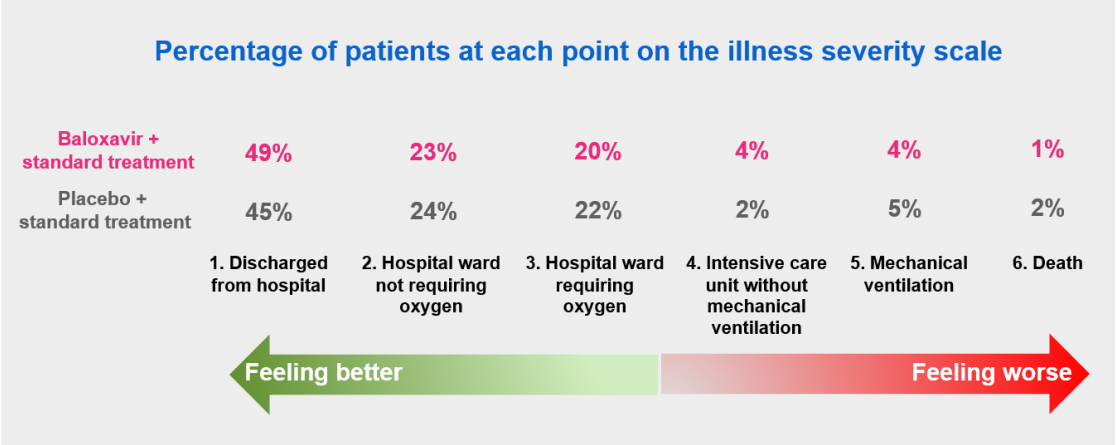
4. What were the results of the study?

Main question: Does adding baloxavir to the standard antiviral treatment for severe flu help people hospitalised with flu to get better quicker?

Researchers looked at how long it took for people with severe flu to get better after their treatment or be discharged from hospital. People who were given baloxavir along with their standard treatment did not see their illness improve any quicker on average than those who received a placebo tablet with their standard treatment.

Other questions: How effective is baloxavir in treating people hospitalised with flu?

Another piece of information that researchers collected was any change in where patients were on a hospital illness severity scale. This tracked where in the hospital the person was being cared for and how much breathing support they required. The percentage of people at each point of the scale was very similar in both treatment groups after 7 days of treatment.



Does baloxavir reduce the presence of the flu virus in the bodies of people hospitalised with flu?

Researchers also looked at something called ‘viral shedding’, where the virus replicates in the body and is released into the environment through coughs and sneezes, where it can infect other people. Researchers wanted to measure when this stopped after treatment. This study found that treatment with baloxavir together with the standard treatment markedly reduced the amount of time that people were shedding infectious virus, compared with treatment with the placebo tablet and the standard treatment.

5. What were the side effects?

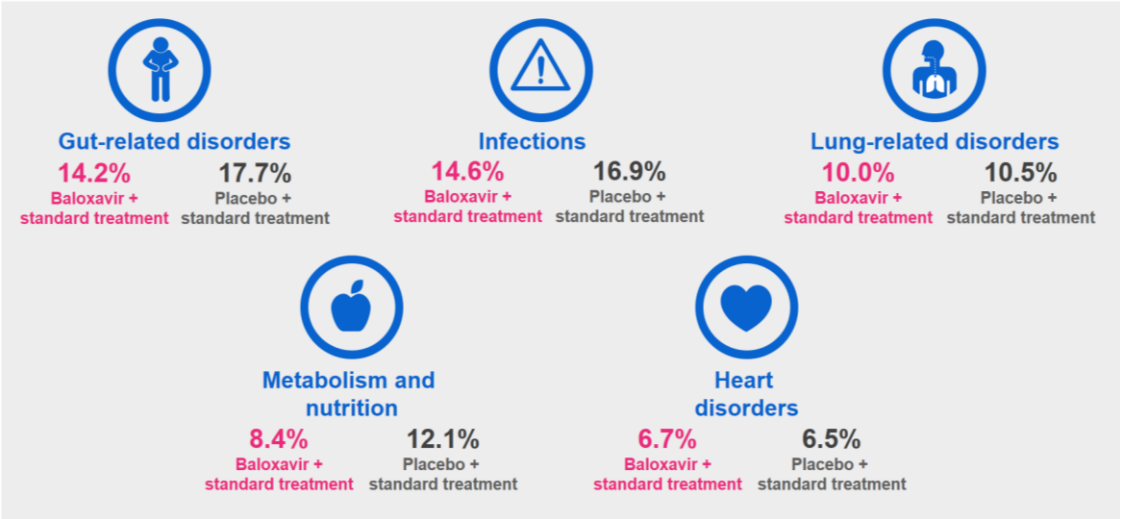
A side effect is any adverse (undesirable) event that a person experiences during the study. These side effects could be due to the flu virus, study treatment (baloxavir), other medications, other illness the patient has or any other reason.

- Side effects may be mild to very serious and can be different from person to person
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other baloxavir studies, or those that appear on the patient information leaflet or package leaflet for the approved medicine

What were the side effects of baloxavir in people hospitalised with flu?

Researchers first looked at the overall number of all reported side effects that people experienced during the study, whether these were caused by the treatment or not. The figure below shows how many people in each group had at least one side effect. The results were similar to those seen in previous studies.

The percentage of people who experienced a side effect was similar between both treatment groups. The figure below shows the proportions of people in each treatment group who experienced different types of side effects.



Then researchers looked at the number of people who had at least one side effect that the person's doctors thought was related to the treatment being given (baloxavir or placebo). The figure below shows that the number of people with side effects believed to be related to the study treatment was low for both groups. Of those side effects believed to be related to the study treatment, only one person had a side effect that was considered to be serious and this person was in the placebo group.

6. How has this study helped research?

These results helped researchers learn more about baloxavir in people hospitalised with severe flu aged 12 years and older.

Key findings from this study:

- Adding baloxavir to standard antiviral treatment for people hospitalised with severe flu did not help patients' illness to improve any quicker than the current standard treatment, or improve where people were on a hospital illness severity scale after a week of treatment
- Baloxavir markedly reduced the time when people shed infectious virus
- No new safety concerns were identified

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 health and treatment.**

7. Are there plans for other studies?

Baloxavir is being studied in many different people. The following studies are still going on:

- miniSTONE-1 is looking at baloxavir in infants younger than 1 year old (https://clinicaltrials.gov/ct2/show/NCT03653364)
- CENTERSTONE is looking at the effect of baloxavir in stopping the spread of flu virus to healthy people aged between 5 and less than 65 years (https://clinicaltrials.gov/ct2/show/NCT03969212)

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/NCT03684044
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001416-30/BG
- https://forpatients.roche.com/en/trials/infectious-diseases/influenza/study-to-assess-efficacy-and-safety-of-baloxavir-marbox-94137.html

You can also read the research article about this study at the link below:

- https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00469-2/fulltext

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-efficacy-and-safety-of-baloxavir-marbox-94137.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 (Roche) who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: Study to Assess Efficacy and Safety of Baloxavir Marboxil In Combination With Standard-of-Care Neuraminidase Inhibitor In Hospitalized Participants With Severe Influenza.

The study is known as 'FLAGSTONE'.

- The protocol number for this study is: CP40617
- The ClinicalTrials.gov identifier for this study is: NCT03684044
- The EudraCT number for this study is: 2018-001416-30