Summary of Clinical Trial Results

A study to find the safest dose of idasanutlin and to see how well it works when given with chemotherapy or venetoclax for children and young adults with leukaemia or solid tumours

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 and
- People who took part in the study.

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

The study started in January 2020 and stopped early – in May 2024 – because too many people had unwanted effects and the medicine being studied did not work as well as expected.

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 treatment for you or your child.

Contents of the summary

Glossary

- AML = acute myeloid leukaemia
- ALL = acute lymphoblastic leukaemia

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about leukaemia, solid tumours and the medicine studied – 'idasanutlin'.

Key information about this study

Why was this study done?

- This study was done to look at how safe potential new treatments for children and young adults who have leukaemia or solid tumours are, and how well they work.
- In this study, people were given the medicine being studied (called 'idasanutlin') either on its own, or with existing medicines ('venetoclax' or chemotherapy).

Who took part?

- This study included 38 people in 6 countries.

What were the results?

- The main findings were:
  - The highest dose of idasanutlin that could be given on its own to children before they had unacceptable unwanted effects from treatment was 4.5mg/kg.
  - The highest dose of idasanutlin that could be given in combination with venetoclax or chemotherapy was not determined. This was because unacceptable unwanted treatment effects were seen when using the lowest doses of idasanutlin that were tested in this study.
  - In the first part of the study, none of the 20 children who had solid tumours with a 'normal' *TP53* gene (a section of DNA), known as *TP53* wild-type ('*TP53* WT') who were treated with idasanutlin on its own had a response to treatment.
  - In the next part of the study, children and young adults with a type of solid tumour called '*TP53* WT neuroblastoma' were treated with idasanutlin combined with other medicines:
    - 1 of the 5 people treated with idasanutlin in combination with chemotherapy (cyclophosphamide and topotecan) had a response to treatment.
    - None of the 4 people treated with idasanutlin in combination with venetoclax had a response to treatment.
  - No one in the study whose tumours were not confirmed to be *TP53* WT had a response to treatment.
- Around 61% of people (23 out of 38 people) taking idasanutlin had serious unwanted effects.
- This study stopped early because too many people had unwanted effects from treatment, and the medicine being studied did not work as well as expected. No one with leukaemia joined prior to the study closing.

1. General information about this study

Why was this study done?

This study looked at new treatments for children and young adults who have leukaemia or solid tumours.

Leukaemia

Leukaemia is a type of blood cancer that often starts in the bone marrow. This study is looking at 2 types of leukaemia known as 'acute myeloid leukaemia' (AML) and 'acute lymphoblastic leukaemia' (ALL).

AML is a blood cancer that affects the bone marrow and the blood cells. In AML, the bone marrow produces too many immature and abnormal white blood cells, red blood cells, and platelets, which can crowd out the healthy blood cells. This can lead to symptoms like fatigue, infections, and bleeding problems.

ALL is also a blood cancer; however, only the white blood cells, blood cells that help fight infections, are affected.

Although treatments for AML and ALL have improved, cancer can still come back – known as a 'relapse'.

Solid tumours

Solid tumours are cancer cells that grow in organ systems throughout the body. In this study, the safety of the study treatments was first looked at in people with solid tumours.

This study also looked at a particular type of solid tumour known as 'neuroblastoma'. Neuroblastoma is a type of cancer that mostly affects young children. It starts in certain nerve cells called neuroblasts, which are found in developing nerve tissue.

Children with neuroblastoma need intensive treatment. This includes chemotherapy (a medicine that kills cancer cells), surgery, high-dose therapy with stem cell rescue, radiation, and immunotherapy. Immunotherapy is a type of medicine that helps a person's own immune system attack cancer cells. The immune system is the body's natural defence, protecting the body from foreign or harmful substances such as bacteria and viruses. However, even with this intensive treatment, children face long-term health issues, such as hearing loss, kidney problems, and hormonal issues, and some children do not survive.

New treatments, or combinations of treatments are needed for AML, ALL and solid tumours, including neuroblastoma.

What were the study medicines?

This study looked at 3 medicines:

- Idasanutlin – the medicine that was studied
- Chemotherapy – existing type of medicine
- Venetoclax – existing medicine.

'Idasanutlin' is the medicine that was studied here – it works in a different way to venetoclax and chemotherapy.

- You say this as 'eye-dess-ah-NUT-lin'.
- Idasanutlin works by activating signals that tell cancer cells to die.
- This means that it could be effective at stopping cancer cells from growing and spreading.
- Idasanutlin was tested at different doses. Some people were treated with idasanutlin by itself and some people were treated with idasanutlin in combination with other treatments.

'Chemotherapy' is an existing type of medicine given to people with cancer.

- Chemotherapy treats cancer by killing fast-growing cells in the body.
- In this study, people with solid tumours were given chemotherapy that has been shown to be active against their type of cancer in previous studies.
- The combinations of chemotherapy medicines used in this study were not approved by health authorities (such as the Food and Drug Administration in the US, or the European Medicines Agency) to be given to children and young adults as part of their treatment for leukaemia or solid tumours.

'Venetoclax' is an existing medicine given to adults with leukaemia.

- You say this as 'ven-et-oh-klaks'.
- Venetoclax is not approved by health authorities to be given to people under 18 years old.
- Venetoclax blocks a protein which helps cancer cells survive. By blocking it, venetoclax can directly kill cancer cells, or help other cancer medicines work better.

What did researchers want to find out?

- Researchers did this study to see how safe idasanutlin is on its own and in combination with other medicines – by checking how many people had unwanted effects and seeing how serious they were when taking each of the medicines during this study (see Section 4 “What were the results of the study?” and Section 5 “What were the unwanted effects?”).
- They also wanted to find out how well the medicines worked (see Section 4 “What were the results of the study?”).

The main questions that researchers wanted to answer were:

1. How safe were different doses of idasanutlin when given on its own or in combination with other medicines?
2. How many people had a reduction of their cancer after treatment?

What kind of study was this?

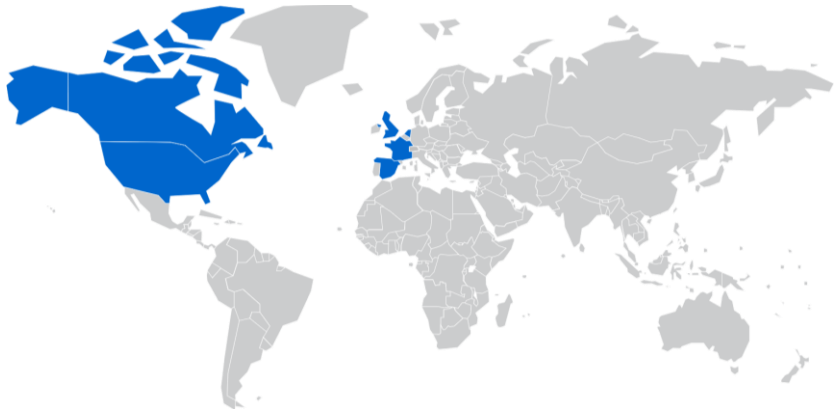
This study was a ‘Phase 1’ study. This was the first study for idasanutlin in children. A small number of children and young adults with cancer took idasanutlin, and the researchers did medical tests on the people who took part to find out more about idasanutlin.

The study was ‘open label’, which means everyone involved, including the participant and the study doctor, knows which study treatment the participant is given.

When and where did the study take place?

The study started in January 2020 and finished in May 2024. This summary was written after the study had ended.

The study took place at 12 study centres – across 6 countries in Europe and North America. The countries were: Canada, France, Netherlands, Spain, United Kingdom and the United States.



2. Who took part in this study?

In this study, 38 people with solid tumours took part. No one with leukaemia joined the study before it was stopped.

People who took part in the study were between 2 and 23 years of age. 22 of the 38 people (58%) were male and 16 of the 38 people (42%) were female.

There were several parts planned for the study (Parts 1a, 1b, 2 and 3). However, Part 2 and Part 3 did not take place.

People could take part in the study if:

- They were less than 30 years old, or less than 18 years old if joining Part 1a
- They had neuroblastoma, leukaemia or a solid tumour (Part 1a only) that did not respond to or had gotten worse after standard treatment.

People could not take part in the study if:

- They had cancer that started in the brain or spinal cord, or cancer that spread to the brain or spinal cord and causes symptoms
- They were pregnant or breastfeeding.

3. What happened during the study?

During the study, people were selected to get 1 of 3 treatments, depending on when they joined the study, and which part they joined.

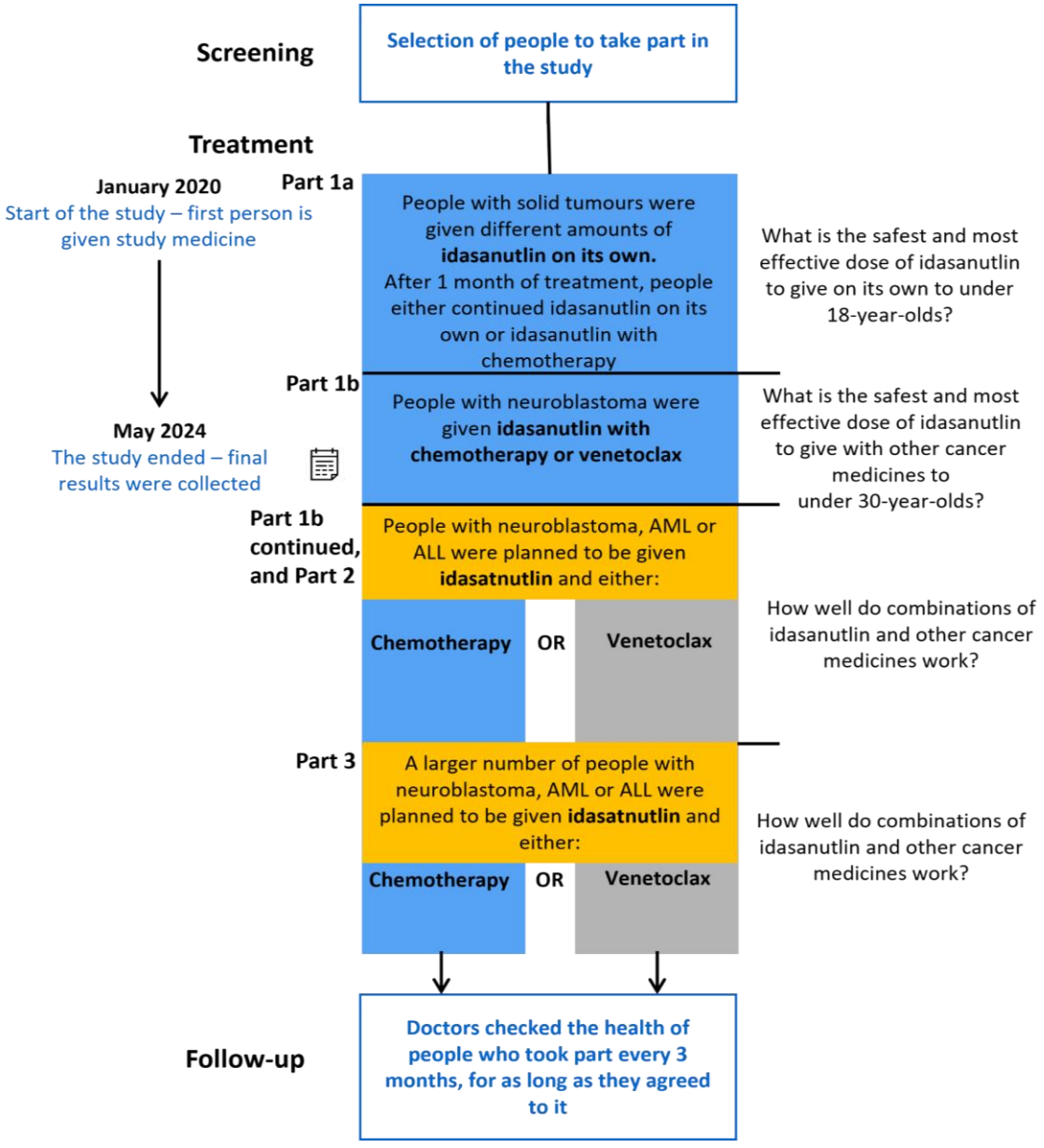
Treatments were given in 'cycles' lasting 28 days each. A treatment cycle is the period of treatment and recovery time before the next set of treatment is given.

People were given either:

- Idasanutlin (the medicine being studied) given on its own by mouth for the first 5 days of each 28-day cycle. These patients had the option to receive chemotherapy (cyclophosphamide and topotecan in combination with idasanutlin after the first cycle).
- Idasanutlin given by mouth for the first 5 days of each 28-day cycle plus venetoclax given by mouth daily.
- Idasanutlin given by mouth plus chemotherapy (cyclophosphamide and topotecan) as a drip into the vein for the first 5 days of each 28-day cycle.

People in the study took the treatment for as long as it could help them, or until they had unacceptable unwanted effects from the treatment, or their disease worsened. 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.

The study flowchart shows all stages planned for the study. This study stopped early, so the symbol on the timeline ( ) shows when the information shown in this summary was collected – after 4 years (May 2024).



4. What were the results of the study?

Question 1: How safe were different doses of idasanutlin when given on its own or in combination with other medicines?

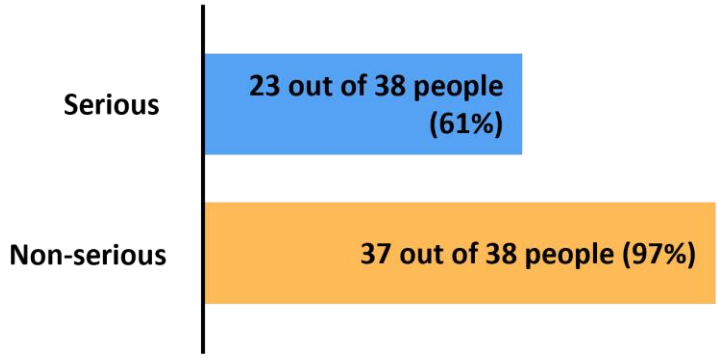
In order to find out how safe different doses of idasanutlin were, researchers looked at the number of people who had unwanted effects and how serious the effects were. An unwanted effect is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.

How many people had unwanted effects?

During this study:

- Around 6 in every 10 people (61%) had at least one serious unwanted effect that was related to the study treatment
- Almost everyone in the study (97%) had an unwanted effect that was not considered serious and that was related to the study treatment.

How many people had unwanted effects, and how serious were they?



Question 2: How many people had a reduction of their cancer after treatment?

Researchers expected idasanutlin treatment to work better against cancers that did not have a change in a gene (a section of DNA) called *TP53*. *TP53* helps repair DNA, or programmes cells to die if the DNA cannot be repaired.

Cancers without a changed *TP53* are known as *TP53* 'wild-type', or '*TP53* WT'.

Researchers looked at the number of people with or without *TP53* WT cancer who had a response to treatment that lasted for at least 1 month.

- None of the 20 people with *TP53* WT solid tumours had a response to treatment with idasanutlin on its own.
- 1 of the 5 people with *TP53* WT neuroblastoma who were given idasanutlin in combination with chemotherapy had a response to treatment.

- None of the 4 people with *TP53* WT neuroblastoma who were given idasanutlin in combination with venetoclax had a response to treatment.

The study was stopped before people with leukaemia were given idasanutlin.

- No one in the study whose tumours were not confirmed to be TP53 WT had a response to 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?

Serious unwanted effects

The most common serious unwanted effects are shown in the following table - these were seen in at least 1 in 5 people across all treatment groups. Some people had more than one unwanted effect – this means that they are included in more than one row in the table.

Serious unwanted effects reported in this study that were thought to be related to the study treatments	**People taking study treatment (38 people total)**
A low level of a type of white blood cell that helps the body fight infections (neutrophils) in the blood, with fever	37% (14 out of 38)
A low level of cells in the blood that help it to clot (platelets)	24% (9 out of 38)

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

During the study, 2 people decided to stop taking their medicine because of unwanted effects.

Most common unwanted effects

The most common unwanted effects that were considered to be related to idasanutlin are shown in the following table – these were seen in at least 1 in 3 people across all

treatment groups. Some people had more than one unwanted effect – this means that they are included in more than one row in the table.

Most common unwanted effects reported in this study that were thought to be related to the study treatments	**People taking study treatment** (38 people total)
A low level of cells in the blood that help it to clot (platelets)	58% (22 out of 38)
Throwing up	53% (20 out of 38)
Wanting to throw up	47% (18 out of 38)
A low number of red blood cells	45% (17 out of 38)
A low level of a type of white blood cell that helps the body fight infections (neutrophils) in the blood	37% (14 out of 38)
A low level of neutrophils in the blood with fever	34% (13 out of 38)
Loose, watery stools	34% (13 out of 38)

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 a single study of 38 people with solid tumours, including neuroblastoma. These results helped researchers learn more about these diseases and idasanutlin.

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.

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at idasanutlin 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/NCT04029688
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-004579-11/results
- https://forpatients.roche.com/en/trials/cancer/a-study-evaluating-the-safety--tolerability--pharmacoki-00443.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/cancer/a-study-evaluating-the-safety--tolerability--pharmacoki-00443.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 I/II, Multicenter, Open-Label, Multi-Arm Study Evaluating The Safety, Tolerability, Pharmacokinetics, and Preliminary Activity of Idasanutlin in Combination With Either Chemotherapy or Venetoclax in The Treatment of Pediatric and Young Adult Patients With Relapsed/Refractory Acute Leukaemias or Solid Tumours”.

The study is known as ‘iMATRIX idasa’.

- The protocol number for this study is: GO40871.
- The ClinicalTrials.gov identifier for this study is: NCT04029688.
- The EudraCT number for this study is: 2018-004579-11.