NOVARTIS

Summary of Clinical Trial Results

A clinical trial to learn about the effects of ruxolitinib when taken with steroids in children and adolescents who got acute Graft versus Host Disease after stem cell transplantation

Protocol number: CINC424F12201

Thank You!

Thanks to the parents, children, and adolescents who participated in this clinical trial to research the treatment **INC424**, also known as **ruxolitinib**. Every participant helped researchers learn more about how **INC424** works in people with a severe condition called **acute Graft vs Host Disease (acute GvHD)**.

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public. We hope this helps the participants understand their important role in medical research.

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If you, your child or adolescent who took part in the clinical trial, have any questions, please ask the doctor or staff at the trial site.

This summary shows the results of a single clinical trial. Other clinical trials may have different findings.

What do these medical words mean?

Acute

A medical problem that happens suddenly and lasts for a short time.

Adverse events

Medical problems that happen during clinical trials. They may or may not be caused by the trial medicine.

Clinical trial

This is a careful experiment overseen by doctors to find out how medicines work.

Clinical trial participant

An adult or child who volunteers to take part in a clinical trial.

Graft vs Host Disease (GvHD)

This illness can happen after someone with unhealthy blood cells (the host) has been injected (transplanted) with someone else's healthy stem cells (the graft). The graft cells are supposed to help make healthy blood cells, but in GvHD, the graft cells attack the host's blood cells instead.

Inflammation

This is a part of the body's defense system. It fights anything that should not be there, like germs. It appears in a part of the body as generally painful, swollen, red, and warm.

Milligram (mg)

A small measure of solid (mg).

Milligram per meter square (mg/m^2)

Unit for measuring the amount of trial drug per unit of body surface area.

Researchers

The people who make research happen. In this trial, these include scientists, your study doctor, and their team.

Ruxolitinib

Pronounced RUX-oh-LI-ti-nib. This is the drug being tested in this trial. It is also known as **INC424**.

Sponsor

A company, hospital, or individual researcher that organizes and pays for the clinical trial.

Stem cells

These are the cells taken from the insides of the bones (bone marrow). They have the ability to help the body make healthy new cells to replace diseased cells.

Stem cell transplant

A medical treatment that involves taking stem cells from a healthy person and injecting them into a person with an illness.

Steroid-resistant (SR)

Steroids (sometimes called corticosteroids) are powerful drugs which help calm down inflammation. Resistant means that the steroids do not work properly, and the inflammation gets worse.

Treatment-naive

A participant who has never received any treatment for a particular medical problem or an illness.

Why was the research needed?

In this trial, researchers wanted to learn about the effects of **INC424** when given along with steroids in children with **acute GvHD** following stem cell transplant.

What is GvHD?

This is a serious condition that may happen after a stem cell transplant. Patients with blood disease undergo stem cell transplant as a treatment. In some cases, the transplanted stem cells (graft) attack the body of the person receiving it (the host). GvHD is a very serious condition that can cause death. GvHD causes:

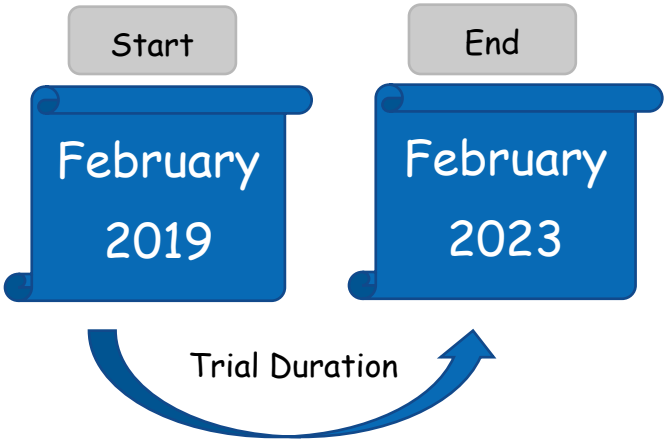
- **itchy rash** that can spread over the body,
- feeling or being sick (**nausea or vomiting**),
- loose poop (**diarrhea**), and

When these occur shortly after a stem cell transplant, it is called **acute GvHD**.

INC424 and how it works

- **INC424**, also known as ruxolitinib, is a drug that is approved in the US, Europe, and multiple other countries for treating acute GvHD in people aged 12 years or older.
- **INC424** blocks a protein in the transplanted stem cells. This stops the stem cells from attacking the body of the host and causing acute GvHD.
- In this trial, researchers wanted to check if **INC424** can give better relief to acute GvHD.

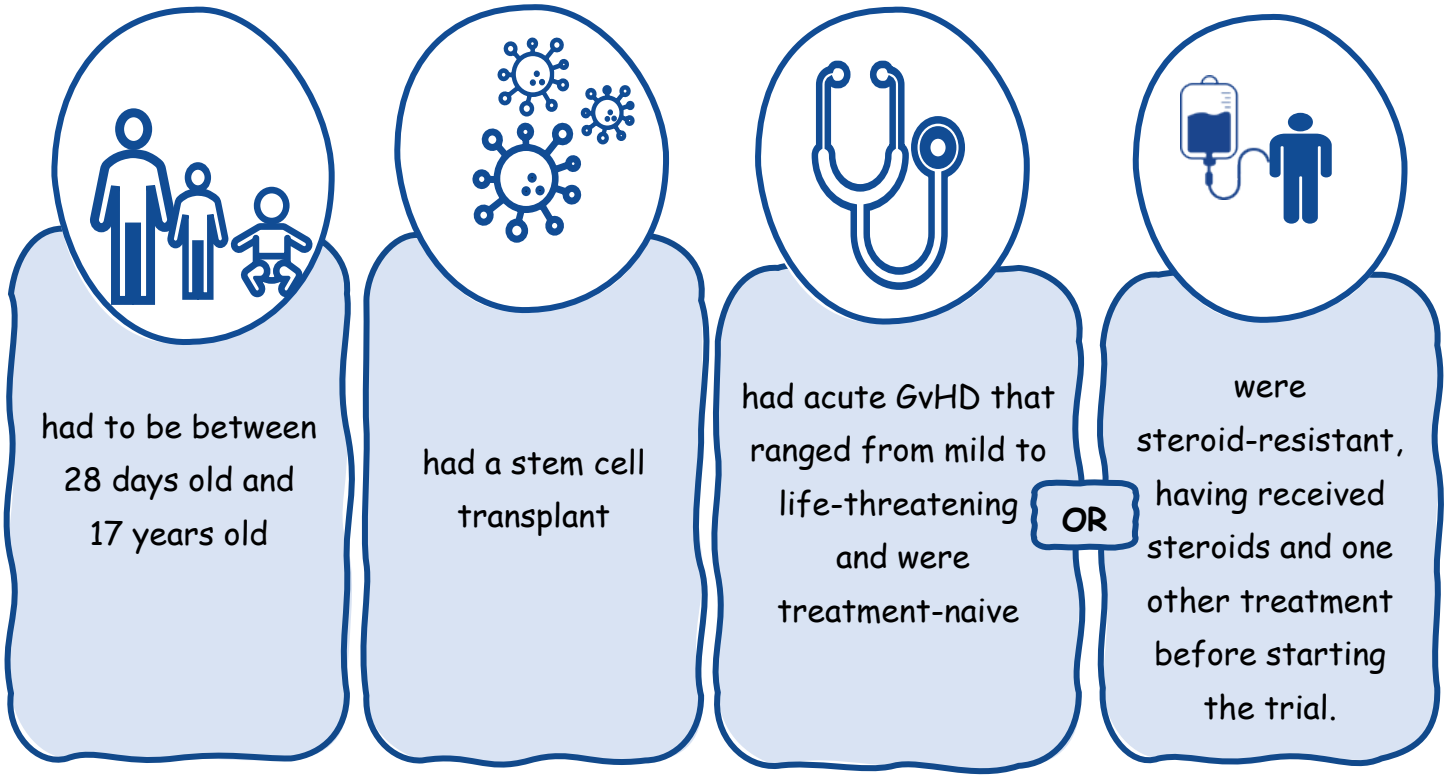
How long was this trial?



The research took 4 years, from the first participant to start until the last one to finish. An individual participant took part for about 2 years.

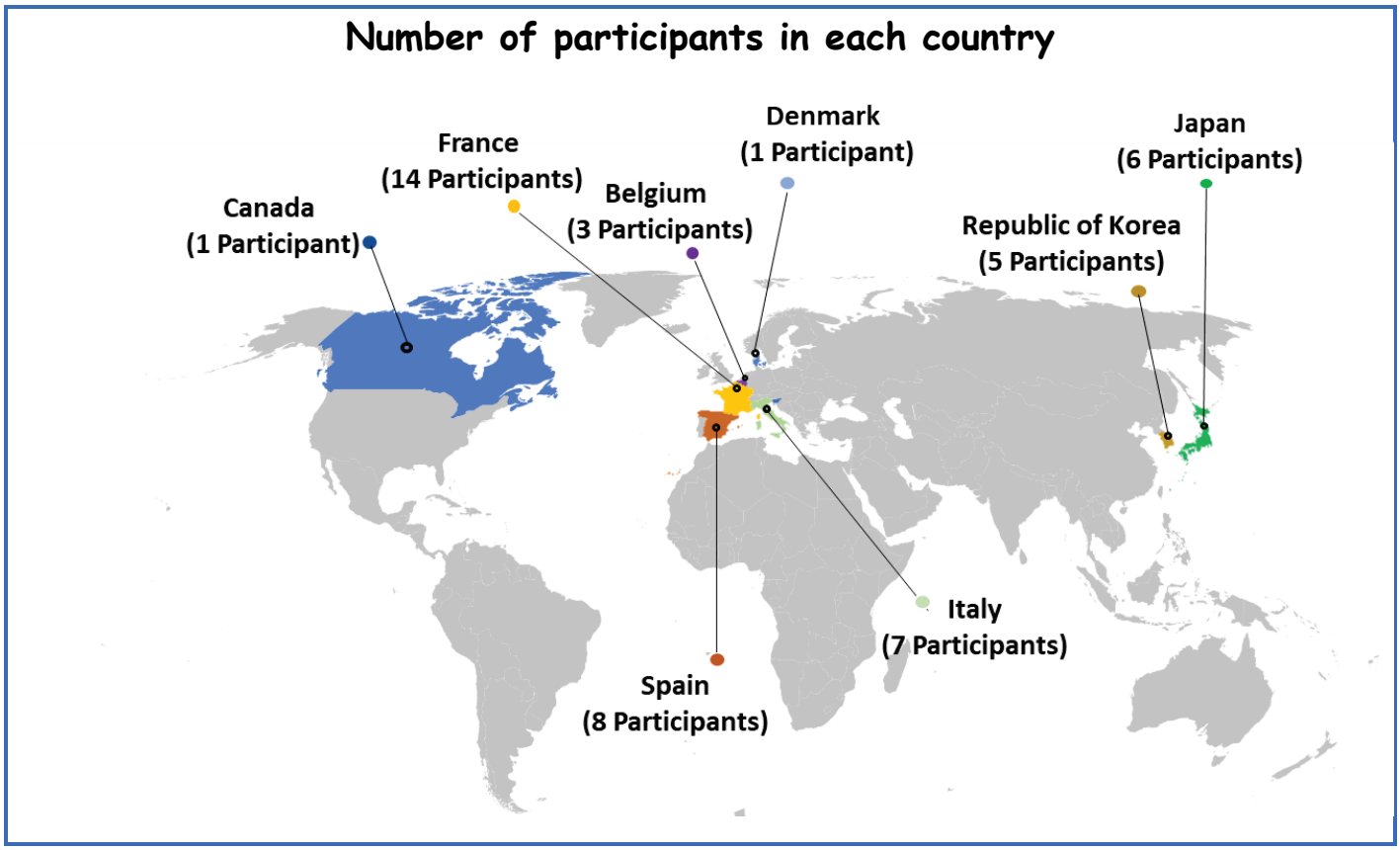
Who was in this trial?

Participants could take part in this clinical trial if it was suitable for them. They:

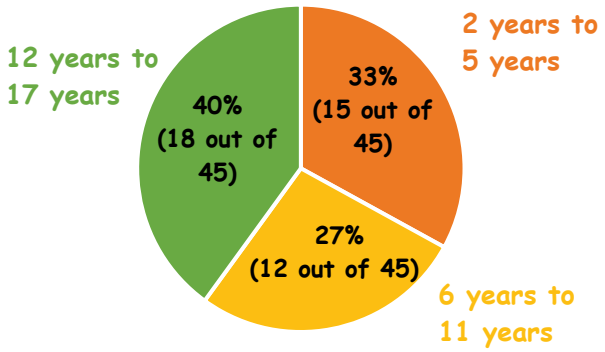


45 participants from 8 countries took part in this trial.

Number of participants in each country



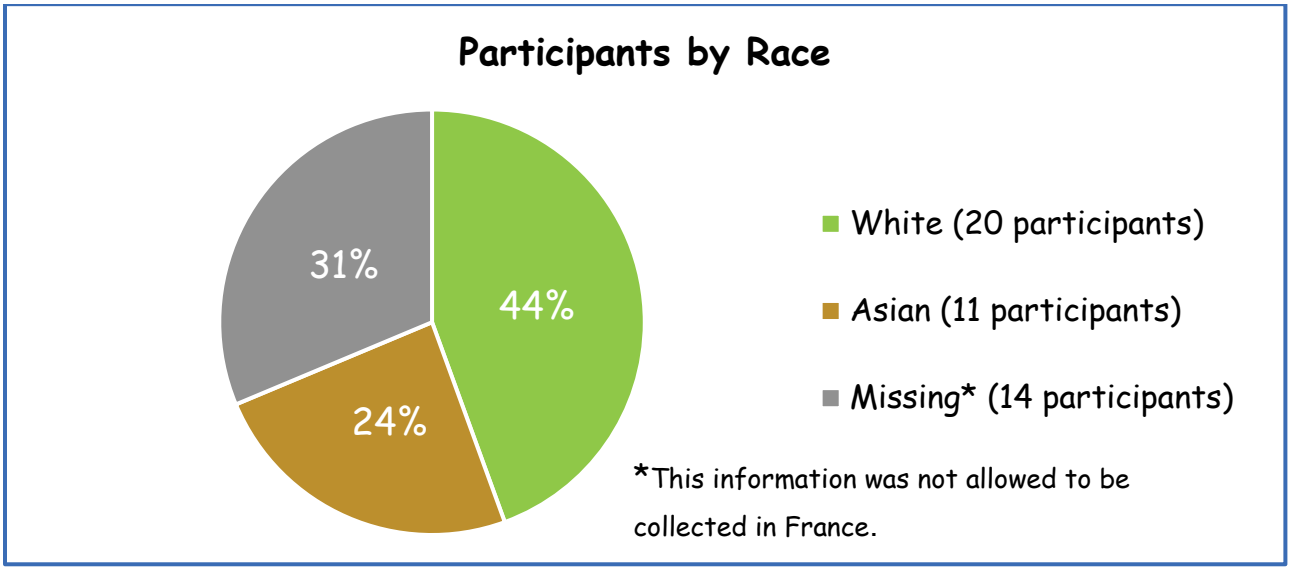
Participants by Age



Participants by Gender

Male: (62%) 28 of 45 participants

Female: (38%) 17 of 45 participants



What treatments did the participants take?

The treatments in this trial were:

	INC424 is taken as a tablet or liquid twice daily. **INC424** is a drug approved in the US, Europe, and multiple other countries for treating acute **GvHD** in people 12 years or older.
	All participants received steroids as standard treatment.

Along with the trial drugs, participants were allowed to take drugs to prevent infections and receive a blood transfusion if required.

What happened during this trial?

Before treatment

Trial doctors checked if participants could take part in the trial.

Up to 1 month

During treatment

The study had 2 parts.

Part 1 tested the amount of **INC424** that goes into the blood, how fast it was removed by the body and how long it stayed in the blood.
The participants were assigned to one of 3 groups based on their age.

Groups	Age	Number of participants	Dose of INC424
Group 1	12 years to 17 years	18	10 mg two times a day
Group 2	6 years to 11 years	12	5 mg two times a day
Group 3	2 years to 5 years	15	4 mg/m^2 two times a day

Up to 6 months

Part 2 tested the effects and safety of **INC424** in participants with acute GvHD. All 45 participants received **INC424** two times a day for 24 weeks at the doses recommended in Part 1 of the study. Participants also received steroids. Participants were either treatment-naive (13 participants) or steroid-resistant (SR) (32 participants).

After treatment

No trial drug was given during this period. All participants continued to receive standard treatment. Researchers monitored the health of participants throughout the trial.

Up to 18 months

What were the main results of this trial?

During Part 1 of the study, the research staff collected samples of blood from the participants at regular time points. They found out:

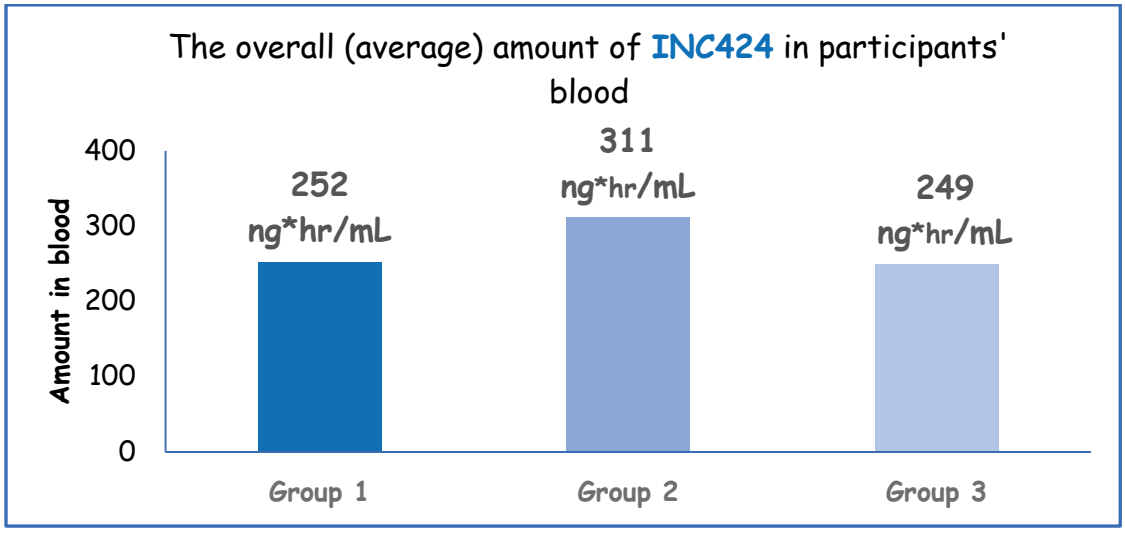
- the overall (average) amount of **INC424** that got into the blood, after it had been swallowed.
- how long it took for the body to remove 50% of **INC424** from the blood.

What do the numbers mean?

A millilitre **(mL)** is a small measure of **liquid**. There are about 5 mL in one teaspoon.

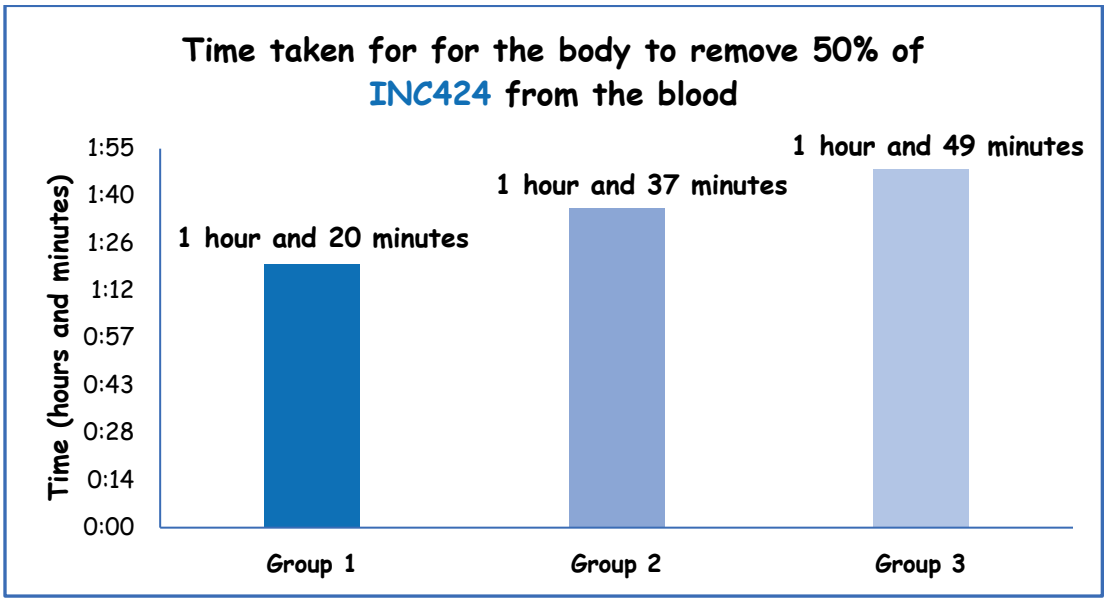
A nanogram **(ng)** is a tiny measure of **weight**. Scientists measured how many ngs of **INC424** were in each ml of each blood sample.

Q **What was the overall amount of INC424 in the blood of participants with acute GvHD?**



The average amount of **INC424** in the participants' blood was similar in all the three age groups.

Q How long it took for the body to remove 50% of INC424 from the blood?



In the three age groups, it took a similar amount of time for the body to remove 50% of INC424 from the blood.

Q What was the recommended safe and appropriate doses of INC424 for the 3 age groups as confirmed by Part 1?

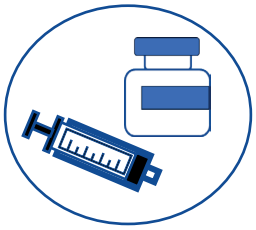
The recommended safe and appropriate dose of INC424 for the 3 age groups are shown in the visual below.

Group 1 (aged 12 to 17 years)

10 mg two times a day

Group 2 (aged 6 to 11 years)

5 mg two times a day



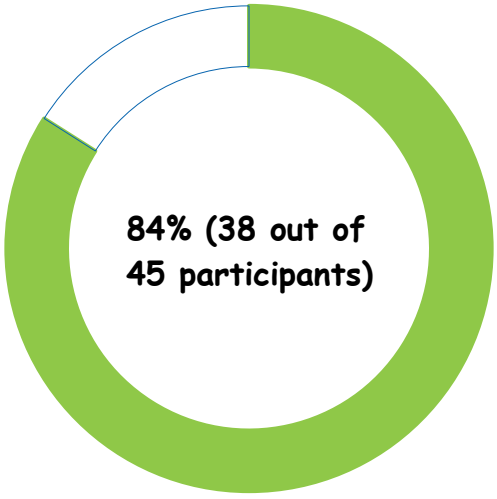
Group 3 (aged 2 to 5 years

4 mg/m^2 two times a day*

*The trial doctors calculated this dose using the height and weight of the child.

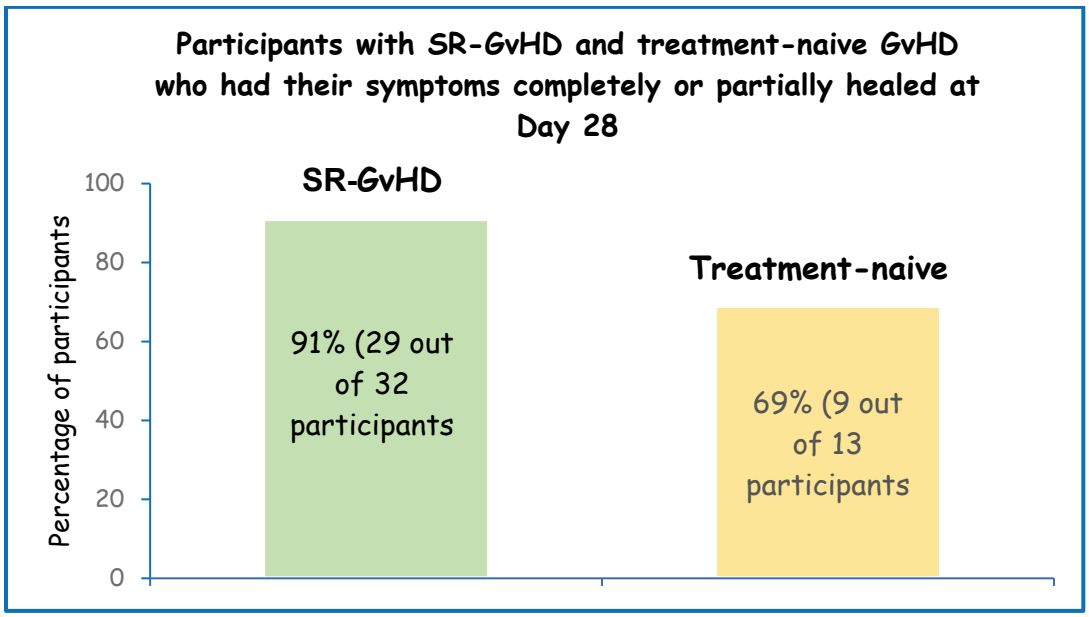
Q In Part 2 of the study, how many participants on INC424 had their acute GvHD symptoms completely or partially healed at Day 28?

Participants with completely or partially healed GvHD symptoms at Day 28



Out of the 45 participants (for all three age groups) in Part 2 of the study who took **INC424**, 38 participants (84%) had their acute GvHD symptoms completely or partially healed at Day 28.

Q How many participants with SR-GvHD had their symptoms completely or partially healed at Day 28 compared to those who were treatment-naive?



At Day 28, 29 out of 32 participants (91%) with steroid resistance and 9 out of 13 treatment-naïve participants (69%) had their symptoms healed completely or partially.

What were the other results of this trial?

Q **In part 2 study, how many participants on INC424 had their acute GvHD symptoms completely or partially healed at Day 28 and remained healed at Day 56?**

Overall, 67% of (30 out of 45) participants on INC424 had their **acute GvHD** symptoms completely or partially healed at Day 28 and remained healed at Day 56.

What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called "**adverse events**."

When new medicines are tested, many clinical trials are needed to find out if the drug causes an adverse event or not.

Researchers keep a careful record of all the adverse events that participants have during a clinical trial.

An adverse event is any sign, symptom, or disease that participants have during a trial. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care. ***These problems may or may not be caused by the trial drug.***

The next section is a summary of the **adverse events** that happened from the start of the trial treatment up to 18 months after the last dose.

How many participants had adverse events?

The **adverse events** that happened during the trial are listed in the table below.

Number of Participants (%) With Adverse Events

The amount of blue area in the long boxes shows the proportion of adverse events for each group.

	Group 1 (Out of **18** participants)	**Group 2** (Out of **12** participants)	**Group 3** (Out of **15** participants)
Age group	12-17 years	6-11 years	2-5 years
At least 1 adverse event	**18** (100%)	**12** (100%)	**15** (100%)
At least 1 serious adverse event	**11** (61%)	**7** (58%)	**6** (40%)
Stopped drug due to adverse event	5(28%)	**3** (25%)	**2** (13%)
Deaths	**6** (33%)	**2** (17%)	**1** (7%)

What were the most common serious adverse events?

The most common **serious adverse events** that happened in at least 2 participants in any group are shown below:

Number of participants (%) with most common serious adverse events

	Group 1 (Out of **18** participants)	**Group 2** (Out of **12** participants)	**Group 3** (Out of **15** participants)
Age group	12-17 years	6-11 years	2-5 years
Decreased kidney function (Acute kidney injury)	**2** (11%)	**0** (0%)	**0** (0%)
Fever (Pyrexia)	**1** (6%)	**1** (8%)	**2** (13%)
Severely low blood pressure due to serious infection (Septic shock)	**2** (11%)	**0** (0%)	**0** (0%)

What other adverse events did the participants have?

The most common other **adverse events** that happened in at least 5 participants in any group are shown below:

Number of participants (%) with other adverse events

	Group 1 (Out of 18 participants)	Group 2 (Out of 12 participants)	Group 3 (Out of 15 participants)
Age group	12-17 years	6-11 years	2-5 years
Increase in a protein called ALT in blood. This means the liver is damaged (Alanine aminotransferase increased)	**5** (28%)	**2** (17%)	**2** (13%)
Low number of red blood cells (Anaemia)	**6** (33%)	**5** (42%)	**9** (60%)
High blood pressure (Hypertension**)**	**2** (11%)	**2** (17%)	**5** (33%)
Decreased neutrophil white blood cell count (Neutropenia)	**6** (33%)	**2** (17%)	**1** (7%)
Decrease in neutrophil white cell count (Neutrophil count decreased)	**5** (28%)	**2** (17%)	**5** (33%)
Low number of platelets* in blood (Platelet count decreased)	**0** (0%)	**2** (17%)	**6** (40%)
Low blood platelet count (Thrombocytopenia)	**6** (33%)	**0** (0%)	**2** (13%)
Lower number of all white blood cells (White blood cell count decreased)	**0** (0%)	**2** (17%)	**5** (33%)

*Platelets are cells in the blood that are involved in stopping any bleeding when we get hurt.

What was learned from this trial?

Researchers found **INC424** to be an effective and safe treatment for children with acute **GvHD**. The overall amount of **INC424** in the blood and the time required by the body to remove 50% of **INC424** was similar in all the age groups. Researchers were also able to find a safe and appropriate dose of **INC424** for children below the age of 12 with acute GvHD.

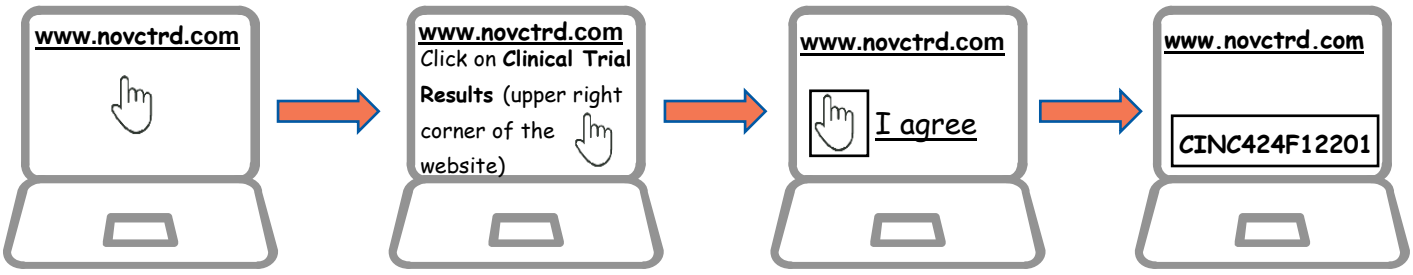
They were also able to recommend a safe dose for children below the age of 2.

INC424 was effective as the first treatment or in combination with standard treatments in participants with acute GvHD. **INC424** was also effective in participants with GvHD who either were treatment-naive or were steroid resistant.

Please remember, this summary only shows the results of a single clinical trial. Other clinical trials may have different results.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com).



You can find more information about this trial on the following websites:

- www.clinicaltrials.gov Use the NCT identifier NCT03491215 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2018-000422-55 in the search field.

Full clinical trial title: A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric subjects with grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

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Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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