Daiichi-Sankyo

Clinical Results Summary

A clinical study to learn about the safety and effects of edoxaban in children with heart conditions who are at risk of blood clots

Protocol number: DU176B-C-U313

Thank You!

Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the children and their parents or carers who took part in this study for edoxaban, also known as DU-176b. Each child helped to advance medical research for children with heart conditions who are at risk of developing blood clots. Their contribution to medicine and healthcare is greatly appreciated.

Important note: This summary only shows the results of a single study. Other studies may have different findings. Researchers and health authorities look at the results of many studies to understand which treatments work and how they work. It takes a lot of people in many studies around the world to advance medical science and healthcare.

Do not use the results of this study to make health decisions. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

What was the main purpose of this study?

Researchers were looking for a better way to treat children with heart conditions who are at risk of developing a type of blood clot called a thromboembolism. These blood clots form in a blood vessel in the body, break loose, are carried by the blood stream and can block another blood vessel. This is a serious condition which can affect different organs in the body. The common symptoms include shortness of breath, pain or swelling in the leg, and reddish discoloration of the affected part of the body.

The main treatment option for thromboembolisms in children are heparins and vitamin K blockers. Heparins are medicines that are used to prevent blood clots. Vitamin K blockers are medicines that are used to reduce clotting of blood by blocking the activity of vitamin K.

Currently, the available medicines for treating blood clots in children have many drawbacks e.g., the medicine has to be given through injections, or close lab monitoring and many dose adjustments are required. Edoxaban is only required to be taken once a day by mouth and does not have any drawbacks as other standard medicines.

In this study, researchers wanted to see how safe and effective edoxaban is at treating children with heart conditions who are at risk of thromboembolism.

Treatments given in this study

The treatments given in this study were:

Edoxaban

An investigational treatment being tested for the treatment of thromboembolism in children with heart conditions

Standard treatment

Heparin (Enoxaparin)

Vitamin K blockers (Warfarin)

Main goals of this study

The main questions the researchers wanted to answer in this study were:

How many children experienced a major bleeding event* or clinically relevant non-major bleeding event** bleeding during this study?

How long after starting treatment did the children who took edoxaban experience a major bleeding event* or clinically relevant non-major bleeding event** compared to those who took standard treatment?

**A major bleeding event is defined as any bleeding occurring in critical parts (like brain, lungs, or stomach) of the body caused by edoxaban or standard treatment.*

*** A clinically relevant non-major bleeding event is defined as any bleeding that does not meet the criteria for major bleeding but requires treatment, hospitalization, or reduction in daily activity.*

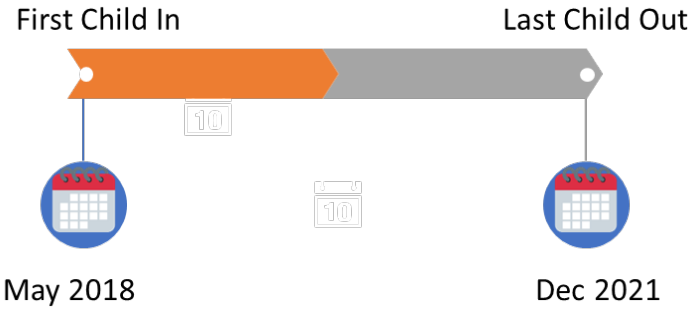
Other goals of this study

Researchers also wanted to answer the following question:

How many children who took edoxaban had a thromboembolic event*** compared to those who took standard treatment?

**** A thromboembolic event is when a blood clot in a blood vessel breaks off and lodges elsewhere in the body, such as the lungs.*

How long was this study?



An individual child could have been in this study for up to 13 months. The study started in May 2018 and ended in December 2021. The results were collected up to December 2021 and a study report was created. This summary is based on that report.

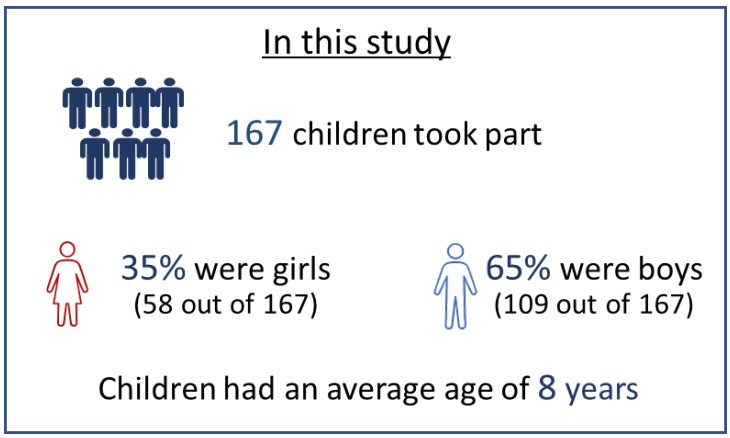
Who was in this study?

This study included 167 children from 16 countries:

Country	No. of children
Egypt	37
USA	33
France	18
Austria	15
Israel	11
Turkey	10
United Kingdom	8
Hungary	7
Lebanon	7
Ukraine	6
Canada	< 5
India	< 5
Russia	< 5
Poland	< 5
Croatia	< 5
Spain	< 5

Children could take part in this study if they:

- had a heart condition and were at a risk of developing clots in the blood vessels and required at least 3 months of treatment to prevent formation of blood clots,
- were not at a risk of bleeding due to taking medicines that help prevent the formation of blood clots,
- did not have mechanical heart valves,
- did not have active bleeding or were not at high risk of bleeding which meant that they were unable to take anticoagulant treatment because it may be harmful.



What happened during this study?

This was a Phase 3 study that compared the safety and effects of edoxaban with standard treatment. In Phase 3 studies, the study treatment is given to a larger number of people with the disease condition to learn more about the effects of the study treatment and its safety.

This study was "open label". This means that both the researchers and the children knew which treatment was given to which children.

This study included 2 treatment periods.

Main treatment period

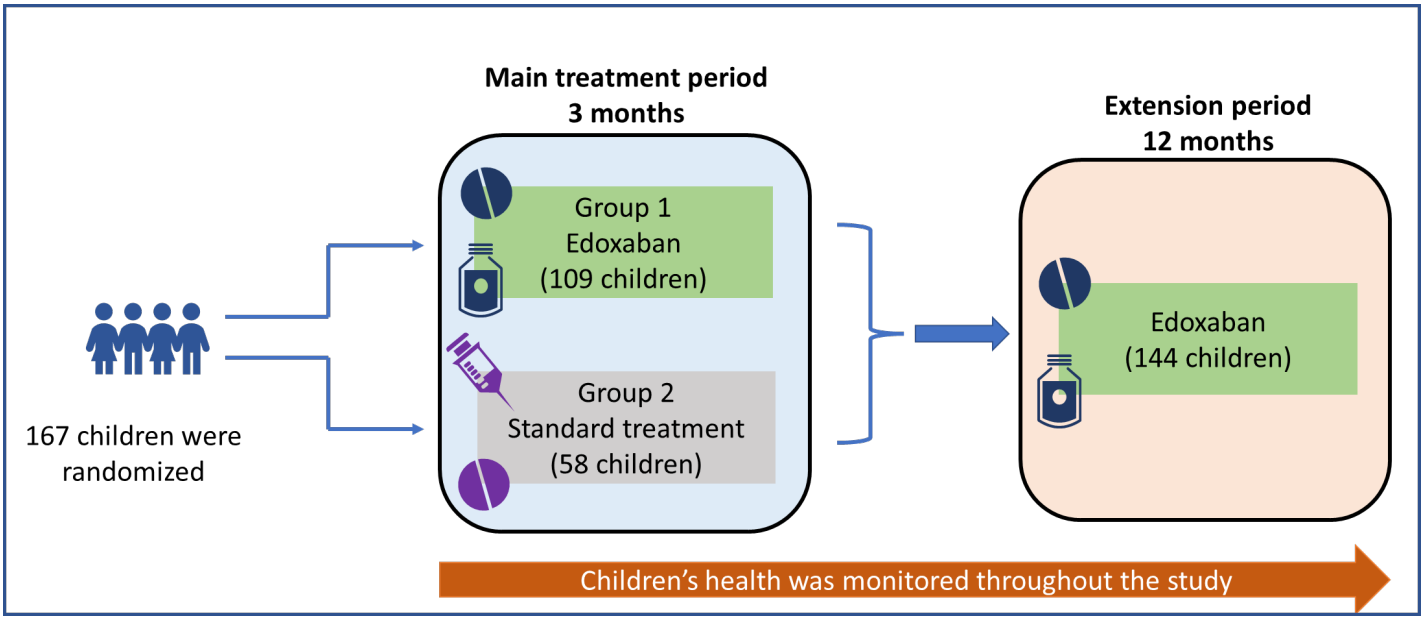
Researchers used a computer system to assign children into two groups by a process called randomization. It means that each child could be assigned to any group, and it helps to make sure the groups are distributed fairly.

The children were divided into the 2 treatment groups:

- Group 1: children received different doses of edoxaban either as a tablet or liquid mixture (suspension), once daily, for 90 days. The doses given to the children were dependent on the age and the weight of the child.
- Group 2: children received either warfarin as a tablet or enoxaparin as an injection under the skin, once daily, for 90 days.

Extension period

In the extension period, all children received different doses of edoxaban either as a tablet or liquid mixture (suspension).



What were the key results of this study?

Key results from this study are shown for the total group of children as average results. This summary does not show the results from each individual child. An individual child's results could be different from the total group of children. A full list of the questions the researchers wanted to answer, and a detailed presentation of the results can be found on the websites listed at the end of this summary.

How many children experienced a major bleeding event or a clinically relevant non-major bleeding event during this study?

The number of children who had major or clinically relevant non-major bleeding events during the **main treatment period** are mentioned in the table below:

Percentage (Number of children) who had major or clinically relevant non-major bleeding events

Edoxaban (Out of 109 children)	Standard treatment (Out of 58 children)
1% (1)	2% (1)

One child on edoxaban had a nosebleed and one child on standard treatment (heparin) had bleeding in the digestive tract. Both events were considered as clinically relevant non-major bleeding events.

During the **extension period**, 1 child (out of 144) had a major bleeding event (liver injury) following an accident, and a non-major bleeding event (nosebleed).

How long after starting treatment did the children who took edoxaban experience a major bleeding event or a clinically relevant non-major bleeding event compared to those who took standard treatment?

During the **main treatment period**, 1 child had a clinically relevant non-major bleeding event 10 days after starting edoxaban and 1 child had a clinically relevant non-major bleeding event 58 days (about 2 months) after starting standard treatment.

During the **extension period**, 1 child had a major bleeding event 224 days (more than 7 months) after starting treatment and a clinically relevant non-major bleeding event 247 days (more than 8 months) after starting treatment.

What were the other results of this study?

How many children who took edoxaban had thromboembolic events compared to those who took standard treatment?

During the main treatment period, 1 child who took standard treatment had 2 thromboembolic events. None of the children who took edoxaban had a thromboembolic event.

During the extension period, 4 children who took edoxaban had a thromboembolic event.

What medical problems did the children have?

Side effects are medical problems (such as a feeling tired) that happened during the study which the study doctor (investigator) thought could be related to the treatments in the study. This section provides a summary of side effects related to the study treatment. The websites listed at the end of this summary has more information about the medical problems that happened in this study.

Side effects are considered serious if they cause death, are life-threatening, cause lasting problems, or require hospitalization. Some children stop study treatment because of side effects.

How many children had serious side effects?

In this study, side effects were monitored for all children who took part in this study.

None of the children had a serious side effect or died due to a side effect during this study.

How many children had non-serious side effects?

During the **main treatment period**, 6% (7 out of 109) of children who were given edoxaban reported side effects and 2% (1 out of 58) of children who were given standard treatment reported side effects. The most common side effect, which happened in at least 2 children in any group, was nosebleed.

The other side effects happened in only 1 child each in any group. These side effects are reported below:

Low blood platelet count, blood in the stool, bruising at the injection site, accidental overdose of treatment, increase in time for blood to clot, increase in the liver test value of alanine aminotransferase in the blood, bleeding in between periods, and blood clot in the artery.

During the **extension period**, 6% (9 out of 144) of children reported side effects. The most common side effects which happened in at least 2 children were headache and nosebleed.

The other side effects only happened in only 1 child each during the **extension period**. These side effects are reported below:

Low blood platelet count, heart attack, blockage of blood flow to the heart muscle, common bruise, liver injury, increase in liver test value of bilirubin, bruising under the skin, and bleeding from a broken blood vessel.

How many children had to stop treatment because of side effects?

During the **main treatment period**, 1 child stopped edoxaban treatment due to blood clot in the artery.

During the **extension period**, 2 children stopped edoxaban treatment due to heart attack and blockage of blood flow to the heart muscle.

How was this study useful for patients and researchers?

This study helped researchers learn about the safety and effects of edoxaban in the prevention of blood vessels being blocked by clots in children with heart conditions.

Findings from this study may be used in other studies with edoxaban. Other studies for edoxaban are ongoing and the sponsor plans to conduct more studies in the future.

Please remember, this summary only shows the results of a single study. Other studies may have different findings. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

Where can I learn more about this study?

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

- www.clinicaltrials.gov: Use the NCT identifier NCT03395639 in the search field.
- www.clinicaltrialsregister.eu/ctr-search/search: Use the EudraCT identifier 2017-000475-90 in the search field.

Please remember that the results on these websites may be presented in a different way. If you were a study child and have questions about the results of this study, please speak with the doctor or staff at your study site.

Full study title: An Open-Label, Randomized, Parallel-Group, Multicenter, Observational Trial to Evaluate the Safety and Efficacy of Edoxaban Tosylate in Children from 38 Weeks Gestational Age to Less than 18 Years of Age with Cardiac Diseases at Risk of Thromboembolic Events.

Sponsor: Daiichi Sankyo, Inc.

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