Daiichi-Sankyo

Clinical Results Summary

A clinical study to learn about the safety and effects of edoxaban compared to standard treatment in children with blood clots

Protocol number: DU176B-D-U312

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 who develop 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 other vessels. This is a serious condition which can affect different organs in the body. It can result in shortness of breath, pain or swelling in the leg, and reddish discoloration of the affected body part.

The main treatment options for thromboembolism 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 the clotting of blood by blocking the activity of vitamin K.

Currently, the available medicines for treating blood clots in children have many drawbacks. For example, the medicine has to be given by an injection, or regular blood tests are required for dose adjustments. The investigational treatment edoxaban, is taken only once a day, by mouth.

In this study, researchers wanted to find out how safe and effective edoxaban was, compared with standard treatment, at treating children who had 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

Standard treatment

Heparin (Enoxaparin)

Activated factor X blocker (Fondaparinux)

Vitamin K blockers (Warfarin)

Main goal of this study

The main question the researchers wanted to answer in this study was:

How many children who took edoxaban had a thromboembolism or died due to a thromboembolism* or had no change in thrombotic burden** compared to those who took standard treatment for 3 months?

** Or for which death due to thromboembolism could not be ruled out.*

*** Thrombotic burden was studied by comparing the size of the blood clot at the start of the study and after 3 months of treatment.*

Other goal of this study

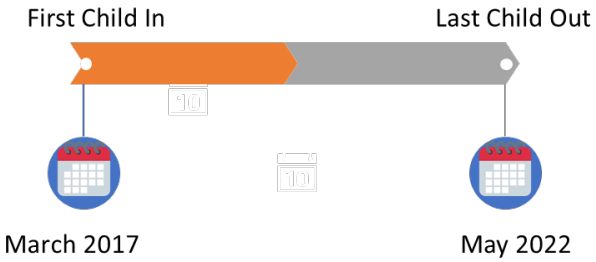
Researchers also wanted to answer the following question:

How many children who took edoxaban experienced a major bleeding event* or clinically relevant non-major bleeding event** compared to those who took standard treatment during the entire study?

**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 a reduction in daily activity.*

How long was this study?



An individual child could have been in this study for up to 13 months. The study started in March 2017 and ended in May 2022. The results were collected up to May 2022 and a study report was created. This summary is based on that report.

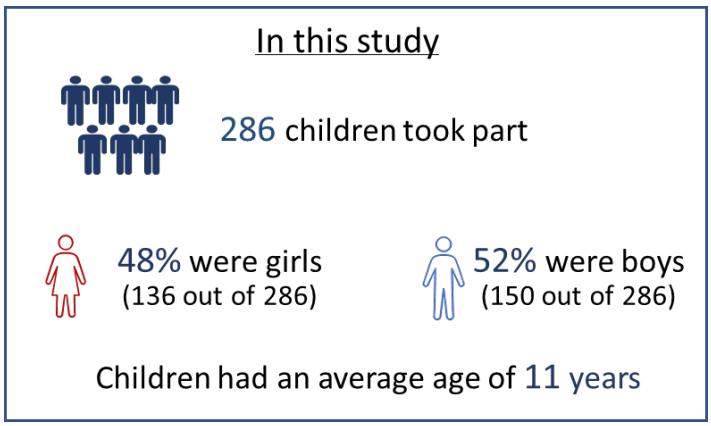
Who was in this study?

This study included 286 children from 29 countries:

Country	No. of children
Brazil	11
Bulgaria	<5
Canada	13
Chile	<5
Columbia	11
Croatia	6
Czech	13
El Salvador	<5
France	5
Germany	8
Guatemala	9
Hungary	23
India	8
Israel	11
Korea	9
Lebanon	9
Malaysia	<5
Netherlands	6
Norway	5
Panama	<5
Portugal	10
Russia	<5
Singapore	6
Spain	10
Taiwan	8
Thailand	15
Turkey	30
Ukraine	<5
United States	40

Children could take part in this study if they:

- were between newborn (pregnancy must have lasted at least 38 weeks) and less than 18 years of age,
- had a confirmed thromboembolism event and required anticoagulant (blood thinner) treatment for 90 days,
- were recently confirmed to have a thromboembolism event and had received heparin for at least 5 days (range 5 to 15 days) before entering the study.



What happened during this study?

This was a Phase 3 study that compared the effects and safety 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 (3 months)

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.

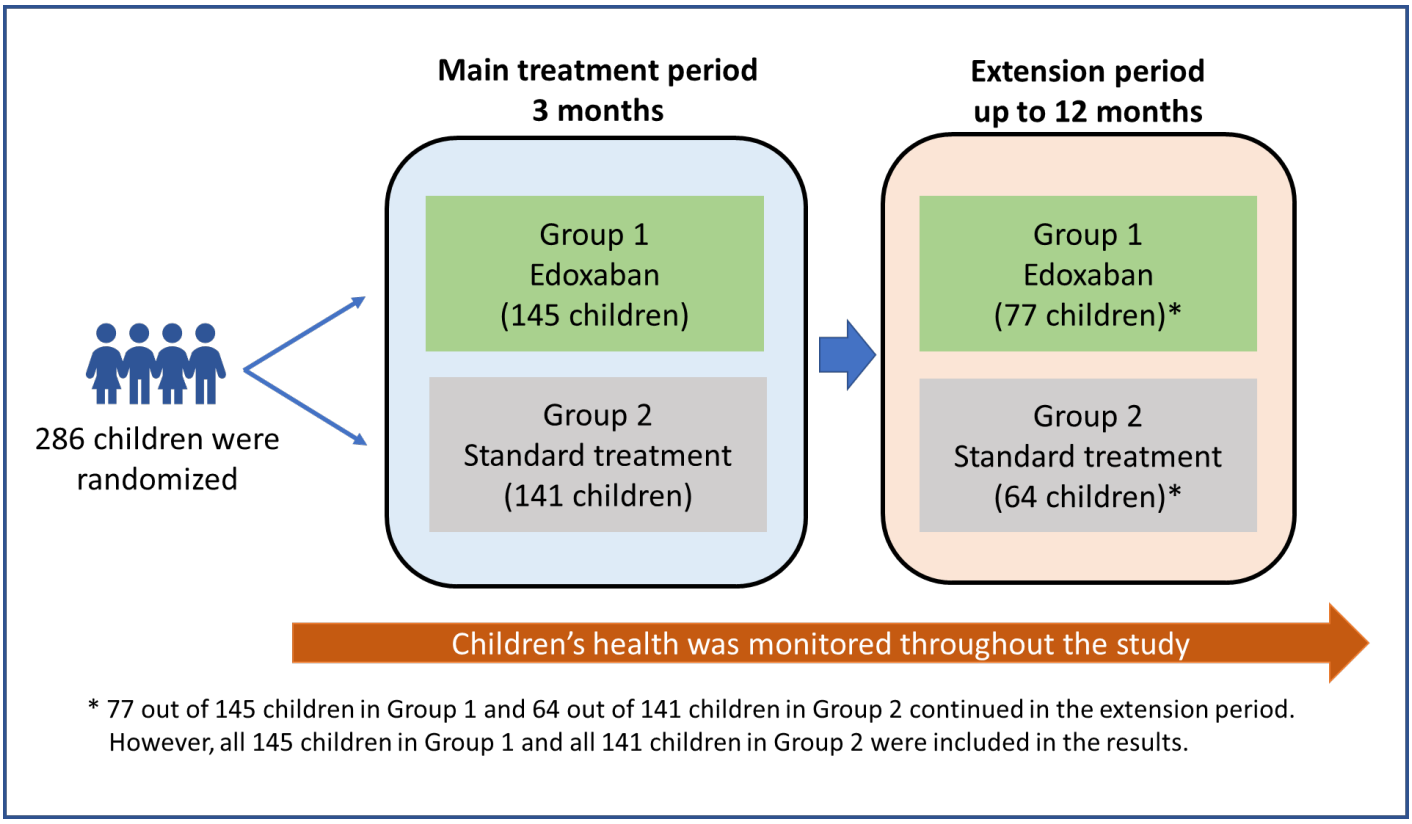
The children were divided into the 2 treatment groups:

- Group 1: children received different doses of edoxaban either as a tablet or liquid mixture (suspension), once daily, for up to 3 months. 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 suspension, enoxaparin or fondaparinux as an injection under the skin, once daily, for up to 3 months.

Extension period (up to 12 months)

If the study doctor decided that a child required further treatment for their thromboembolism, then the child could continue taking edoxaban or standard treatment for up to 12 months during the extension period.

When a child stopped taking treatment after 3 months, or longer if they continued to the extension period, they were monitored by the study doctors for a further 30 days for any side effects.



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 who took edoxaban had a thromboembolism or died due to a thromboembolism* or had no change in thrombotic burden** compared to those who took standard treatment for 3 months?

The number of children who had a thromboembolism or died due to a thromboembolism or had no change in thrombotic burden during 3 months of treatment are shown in the table below.

Event	**Edoxaban** Number of children out of 145 (Percentage)	**Standard treatment** Number of children out of 141 (Percentage)
Thromboembolism, death due to thromboembolism*, and no change in thrombotic burden**	26 (18%)	31 (22%)
Thromboembolism	5 (3%)	2 (1%)
Death due to thromboembolism*	1 (<1%)	1 (<1%)
No change in thrombotic burden**	21 (15%)	29 (21%)

** Or for which death due to thromboembolism could not be ruled out.*

*** Thrombotic burden was studied by comparing the size of the blood clot at the start of the study and after 3 months of treatment.*

What was the other result of this study?

How many children who took edoxaban experienced a major bleeding event* or clinically relevant non-major bleeding event** compared to those who took standard treatment during the entire study?

10 out of 145 (7%) children on edoxaban and 5 out of 141 children (4%) on standard treatment had both a major bleeding event and a clinically relevant non-major bleeding event during the entire study.

**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 a reduction in daily activity.*

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.

3 out of 145 (2%) children who were given edoxaban had serious side effects of bleeding into the lung, itchy skin and blockage of a blood vessel.

3 out of 141 (2%) children who were given standard treatment had serious side effects of blood in vomit, passing of blood in stool and increased liver enzymes.

These serious side effects happened in only 1 child each in any group.

How many children had non-serious side effects?

24 out of 145 (17%) of the children who were given edoxaban and 20 out of 141 (14%) of children who were given standard treatment had non-serious side effects.

The most common non-serious side effects, which happened in 3 or more children on edoxaban, were nosebleed and headache.

The most common non-serious side effects, which happened in 3 or more children on standard treatment, were nosebleed and bleeding from the uterus.

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

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

2 children stopped edoxaban treatment because of side effects of itching and new thromboembolism. 1 child stopped standard treatment because of side effects of increased in liver enzymes.

How was this study useful for patients and researchers?

This study helped researchers learn about the effects and safety of edoxaban in treating children who develop blood clots.

Findings from this study may be used in other studies with edoxaban. However, the sponsor has no plans to conduct more studies on the use of edoxaban in children with thromboembolism.

Please remember, this summary only shows the results of a single study. Other studies may have different results or conclusions. Please talk to a doctor for further information

Where can I learn more about this study?

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

- www.clinicaltrials.gov: Use the NCT identifier NCT02798471 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: A Phase 3, Open-Label, Randomized, Multicenter, Controlled Trial to Evaluate the Pharmacokinetics and Pharmacodynamics of Edoxaban and to Compare the Efficacy and Safety of Edoxaban with Standard-of-Care Anticoagulant Therapy in Pediatric Subjects from Birth to Less Than 18 Years of Age with Confirmed Venous Thromboembolism (VTE).

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