CLINICAL TRIAL RESULTS

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medicine works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Fragmin®(Dalteparin Sodium Injection)

Compound Number PN180524

Protocol Number: A6301094

Dates of Trial: 20 August 2009 to 20 March 2018

Title of this Trial: A Three Month Prospective Open Label Study of Therap With Fragmin® (Dalteparin Sodium Injection) in Children With Venous Thromboembolism With or Without Malignancies

Date of this Report: 19 February 2019

– Thank You –

Pfizer, the Sponsor, would like to thank you and your child for participating in this clinical trial and provide you a summary of results representing everyone who participated. If you have any questions about the study or results, please contact the doctor or staff at your child's study site.

WHY WAS THIS STUDY DONE?

"Venous thromboembolism", or VTE, is the name for a blood clot that forms in the body. VTE can happen in a vein located in different parts of the body, including the legs, the arms, the groin, the lungs, or other parts of the body. A VTE can be life-threatening if not treated.

Certain children may be more likely to have a VTE, such as those with cancer or other serious conditions that require hospitalization. VTE may be treated or prevented with a type of medicine called an "anticoagulant", also known as a "blood thinner". One anticoagulant that is used is called dalteparin. It is given as an injection under the skin. Dalteparin has been approved for use in adults with VTE in the United States and Europe, but has not been approved in children because additional studies are needed to find out if dalteparin could be a useful medicine for children.

The main purpose of this study was to learn more about the use of dalteparin in children with or without cancer, and to help determine the appropriate dose of dalteparin for treating VTE in children. The study doctors collected blood samples from the children and did a blood test to find out what the "anti-Xa level" was after certain doses of dalteparin were given. The Anti-Xa level shows how well dalteparin makes blood clots go away or stops a blood clot from forming.

Specifically, the study doctors wanted to answer these questions:

- **What effect would dalteparin, given at different doses, have on the bodies of children, including children with cancer and children without cancer?**
- **What would be the average dalteparin dose required to treat VTE in children, based on age and weight?**
- **How long did it take the children's anti-Xa test results to reach target levels?**

WHAT HAPPENED DURING THE STUDY?

This study was done to learn more about the use of dalteparin in children who have a VTE. The children who entered the study had to have VTE, and may also have had a

type of cancer.

First, the children were checked by the study doctor to make sure they were a good fit for the study. This was called "screening".

The children were grouped by age:

- Group 1 (1 child): 0 weeks old to less than 8 weeks old
- Group 2 (2 children): At least 8 weeks old, but less than 2 years old
- Group 3 (8 children): At least 2 years old, but less than 8 years old
- Group 4 (7 children): At least 8 years old, but less than 12 years old
- Group 5 (20 children): At least 12 years old, but less than 19 years old

This was an "open label" study, which means that the children, their parents/guardians, and the study doctors knew which medicine the children received during the study. In this study, all children received dalteparin.

There were 3 phases to this study. Phase 1 was known as the "dose adjustment phase". This phase started when the child received their first (starting) dose of study medicine and continued for up to 7 days.

The starting dose depended on the age and weight of the child, as follows:

- Group 1: 125 IU per kilogram (kg) of weight
- Group 2: 150 IU per kg of weight
- Group 3: 125 IU per kg of weight
- Group 4: 125 IU per kg of weight
- Group 5: 100 IU per kg of weight

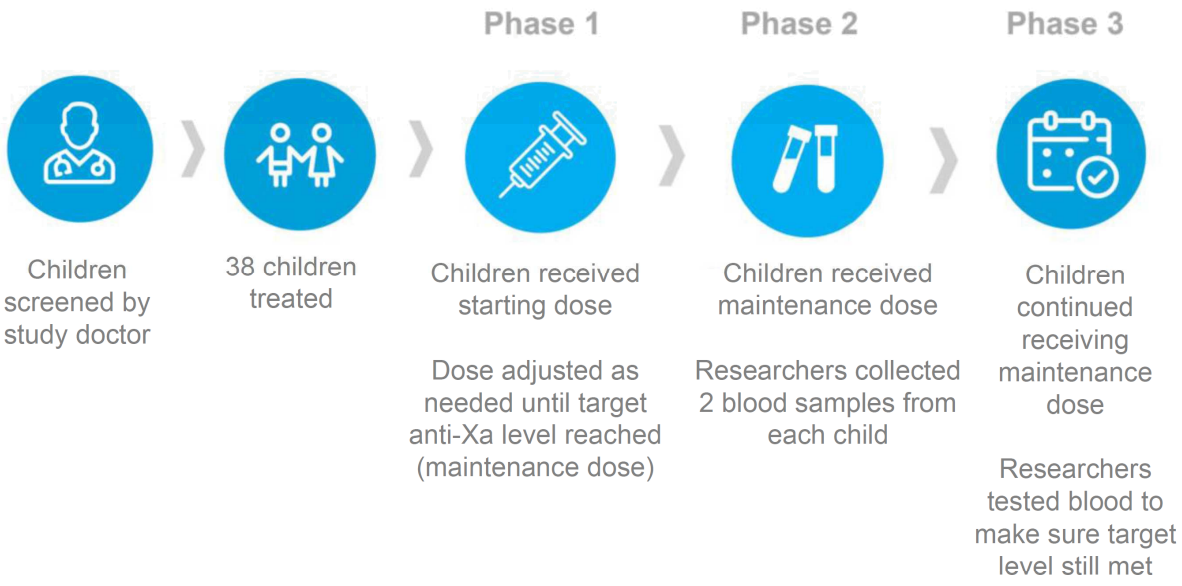
Then, during this 7-day "dose adjustment phase", the study doctors tested the child's anti-Xa levels. Each child's dalteparin dose was adjusted (upward or downward), as needed, until the child's anti-Xa test result was between 0.5 and 1.0 (the "target" range). The dose that put the child's anti-Xa level into that target range is called the "maintenance dose". This is the dose that would be used going forward, in order to keep the child's anti-Xa level within the target range.

Once the children had reached the target anti-Xa level, they entered Phase 2 of the

study. Phase 2 was known as the "pharmacodynamics phase", and it lasted between 1 and 7 days (enough time to collect 2 blood samples from each child). During this time, children received their maintenance dose from Phase 1, given every 12 hours.

After they completed Phase 2, the children entered Phase 3 of the study. Phase 3 was known as the "follow-up phase", and it lasted until the end of the study. The children continued receiving their maintenance dose of dalteparin, given every 12 hours. The study doctors tested the children's blood to make sure anti-Xa was still within the target range (0.5 to 1.0).

The figure below shows what happened during this study.



*Children were monitored for medical problems throughout study

While children were only in the study for up to 90 days, the entire study took almost 9 years to complete. The sponsor ran this study at 15 locations in Norway, Russia, Slovenia, Spain, and the United States. It began 20 August 2009 and finished 20 March 2018. A total of 14 girls and 24 boys participated All children were between the ages of 0 and 18 years old.

The study required the children to come to a total of 7 visits at the study center. Of the 38 children who were treated in the study, 26 children (68%) completed all of the

study visits. At total of 12 children (32%) did not finish the study, either due to medical problems or by their parent/guardian's choice.

When the study ended in March 2018, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

WHAT WERE THE RESULTS OF THE STUDY?

What effect did dalteparin, given at different doses, have on the bodies of children, including children with cancer and children without cancer?

To answer this question, the researchers looked at the children's anti-Xa levels. Most of the children in this study were able to reach target anti-Xa levels. However, the younger children needed a higher dose of dalteparin to reach these levels, compared to the older children. For instance, children from Group 2 needed an average dose of 207.5 IU per kg of weight, while children from Group 4 needed an average dose of 116.7 IU per kg of weight.

What was the average dose of dalteparin required to treat VTE in children, based on age and weight?

To answer this question, the researchers looked for the average dose of dalteparin needed to reach anti-Xa target levels in each age group. The average doses needed were as follows:

- Group 2: 207.5 IU per kg of weight
- Group 3: 128.15 IU per kg of weight
- Group 4: 125 IU per kg of weight
- Group 5: 116.7 IU per kg of weight

There was only 1 child in Group 1, and this child did not reach the anti-Xa target level during the study. Therefore, the researchers were not able to determine the average dose needed to reach anti-Xa target levels (treat VTE) for this age group.

How long did it take the children's anti-Xa test results to reach target levels?

To answer this question, the researchers measured how long it took for the children's anti-Xa tests results to reach levels between 0.5 and 1.0, which was the target range. On average, it took 2.6 days for the children's anti-Xa tests results to reach this range.

This does not mean that everyone in this study had these results. Other studies may produce different results, as well. These are just some of the main findings of the study, and more information may be available at the websites listed at the end of this summary.

WHAT MEDICAL PROBLEMS DID CHILDREN HAVE DURING THE STUDY?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment, or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what the side effects of an experimental drug might be.

If any new medical problems arose during the study, these were reported by the study doctors. In addition, if a preexisting medical problem worsened, these would also be reported.

Out of 38 children in this study, 33 children (87%) had at least 1 medical problem. The most common medical problems are listed below.

Most Common Medical Problems (Reported in 2 or More Children)	
Medical Problem	**Number of Children (38 Children Treated)**
Bruising at site where medicine was injected	15 (39%)
Low number of red blood cells	7 (18%)
Fever	7 (18%)
Vomiting	6 (16%)
Bruising	6 (16%)
Headache	6 (16%)
Pain in throat	6 (16%)
Fast heart rate	5 (13%)
Diarrhea	5 (13%)
Low number of a type of white blood cell called a neutrophil	4 (11%)
Nausea	4 (11%)
Stomatitis	4 (11%)
Pain at site where medicine was injected	4 (11%)
Inflammation (swelling) of the mucous membranes	4 (11%)
Low level of calcium in blood	4 (11%)
Nosebleed	4 (11%)
Hair loss	4 (11%)
Low number of platelets in the blood	3 (8%)
Swelling of body tissues, usually in the legs, feet, and ankles	3 (8%)

Low level of potassium in blood	3 (8%)
Joint pain	3 (8%)
Pain in hands or feet	3 (8%)
Cough	3 (8%)
High blood pressure	3 (8%)
Low number of white blood cells	2 (5%)
Dry eye	2 (5%)
Tear in the tissue lining the anus (anal fissure)	2 (5%)
Constipation	2 (5%)
Bleeding gums	2 (5%)
Vomiting blood	2 (5%)
Blood in stool	2 (5%)
Feeling tired	2 (5%)
Swelling caused by a collection of blood at site where medicine was injected (hematoma)	2 (5%)
Bleeding at site where medicine was injected	2 (5%)
Swelling at site where medicine was injected, caused by an overgrowth of tissue (nodule)	2 (5%)
Low level of sodium in blood	2 (5%)
Low level of phosphate in blood	2 (5%)
Feeling dizzy	2 (5%)
Pain caused by nerve damage	2 (5%)
Numbness and pain in arms, hands, feet, and legs caused by nerve damage	2 (5%)

Runny nose	**2 (5%)**
Skin rash caused by touching something you are allergic to	**2 (5%)**
Bleeding under the skin, which causes the skin to be discolored	**2 (5%)**
Redness of skin	**2 (5%)**
Skin pain	**2 (5%)**

WERE THERE ANY SERIOUS MEDICAL PROBLEMS?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

Out of 38 children in this study, 21 children (55%) had new serious medical problems that were diagnosed during the study. One child passed away during the study. The study doctor determined that this child passed away due to a condition that was present before the study started and not related to taking dalteparin.

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

If you have questions about the results of your study, please speak with the doctor or staff at your child's study site.

For more details on this study protocol, please visit:

www.clinicaltrials.gov Use the study identifier **NCT00952380**

www.clinicaltrialsregister.eu Use the study identifier **2016-000394-21**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients. There is an ongoing study in which pediatric patients could receive Fragmin to treat VTE.

Again, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!