Clinical Study Results

Research Sponsor: AstraZeneca

Drug Studied: Dapagliflozin

Study Title: A study to learn how dapagliflozin affects the HbA1c levels in people with type 1 diabetes who are already taking insulin

Thank you!

Thank you to the participants who took part in the clinical study for the drug dapagliflozin. You and all of the participants helped researchers learn more about dapagliflozin to help people with type 1 diabetes.

AstraZeneca sponsored this study and thinks it is important to share the results of the study with you and the public. An independent, non-profit organization called CISCRP helped prepare this summary of the study results for you. We hope it helps you understand and feel proud of your important role in medical research.

If you participated in the study and have questions about the results, please speak with the doctor or staff at your study site.

What is happening with the study now?

Participants were in the study for up to 68 weeks. But, the entire study took about 3 years to finish. The study started in July 2015 and ended in April 2018. The study included 815 participants in Argentina, Belgium, Canada, Chile, Germany, Japan, the Netherlands, Poland, the Russian Federation, Sweden, Switzerland, the United Kingdom, and the United States.

Two participants left the study before they took any medicine. This summary discusses 813 of the 815 participants.

The sponsor reviewed the data collected when the study ended and created a report of the results. This is a summary of that report.

Why was the research needed?

Researchers are looking for a way to help people with type 1 diabetes to control their blood sugar. Before a drug can be approved for people to take, researchers do clinical studies to find out how it works and how safe it is.

In this study, the researchers wanted to find out if dapagliflozin works in a large number of participants with type 1 diabetes who are already taking insulin. They also wanted to find out if the participants had any medical problems during the study.

Insulin is a substance made by the body. It controls the amount of sugar in the blood. In people with type 1 diabetes, the body makes either little or no insulin. This causes the amount of sugar in the blood to become too high. High blood sugar levels can lead to medical problems including damaged eyesight, damaged kidneys, heart attack, and stroke.

In this study, the researchers wanted to learn what happened to the participants' blood sugar levels when they took dapagliflozin. To find out, researchers measured the levels of hemoglobin A1c, also called HbA1c, in the participants' blood. The HbA1c test measures how much blood sugar is bound to a protein called hemoglobin that is found in red blood cells.

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

- How did dapagliflozin taken with insulin affect the HbA1c levels in the participants' blood?
- Did dapagliflozin taken with insulin affect the participants' type 1 diabetes in other ways?
- What medical problems did the participants have during the study?

To answer the questions in this study, the researchers asked for the help of men and women with type 1 diabetes. The participants in this study were 18 to 75 years old.

What kind of study was this?

This was a “double-blind” study. This means none of the participants, doctors or other study staff knew what treatment each participant took. Some studies are done this way because knowing what treatment the participants are taking can affect the results of the study. When the study ended, the research sponsor found out which treatment the participants took so they could create a report of the study results.

The participants in the study were already taking insulin. During the study, the participants also took either dapagliflozin or a placebo.

A placebo looks like the study drug but does not have any medicine in it. Researchers use a placebo to help make sure any of the effects they see in the participants who take a treatment are actually caused by that treatment.

A computer program was used to randomly choose the treatment each participant took. This helps make sure the groups are chosen fairly. Researchers do this so that comparing the results of each treatment is as accurate as possible.

What happened during the study?

Before the study started, the participants visited their study site 5 times over the course of up to 12 weeks. During these visits, the doctors:

- did a physical examination
- took urine samples
- checked the HbA1c levels of the participants
- checked the participants’ blood sugar levels throughout the study
- asked the participants about their medical history, how they were feeling, and what medicines they were taking

Before the participants took treatment, the participants filled out questionnaires about how they were feeling.

During the study, the participants visited their study site up to 14 more times over the course of 52 weeks. The researchers also called the participants 3 times during the study to ask the participants about their overall health and how they were feeling.

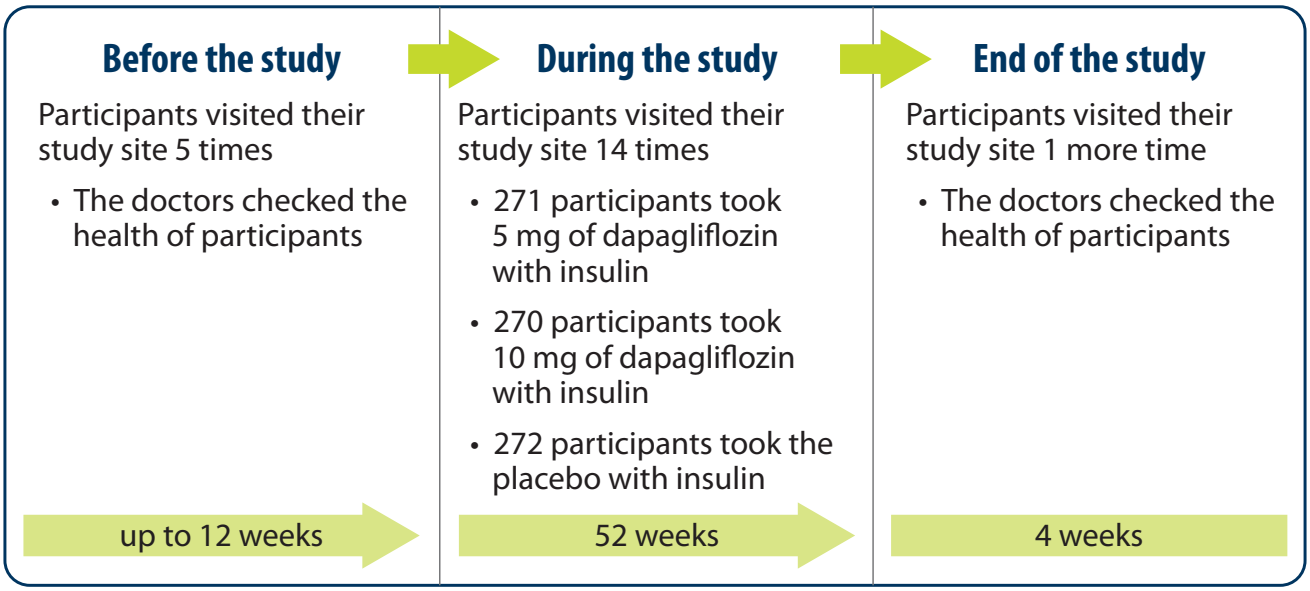
During the study, the participants took their treatment once a day for 52 weeks. Doses of dapagliflozin were measured in milligrams, also called mg. Participants took 1 of the following treatments in tablet form by mouth:

- 5 mg of dapagliflozin with insulin
- 10 mg of dapagliflozin with insulin
- placebo with insulin

After 24 and 52 weeks of treatment, the participants filled out questionnaires about how they were feeling.

At the end of the study, the participants visited their study site once up to 4 weeks after their last dose. During this visit, the doctors checked the participants' overall health and asked how they were feeling.

The chart below shows how the study was done.



What were the results of the study?

This is a summary of the main results from this study overall. The results each participant had might be different and are not in this summary. A full list of the questions the researchers wanted to answer can be found on the websites listed at the end of this summary. If a full report of the study results is available, it can also be found on these websites.

Researchers look at the results of many studies to decide which treatments work best and are safest. Other studies may provide new information or different results. Always talk to a doctor before making any treatment changes.

How did dapagliflozin taken with insulin affect the HbA1c levels in the participants' blood?

Overall, the researchers found that the participants who took dapagliflozin with insulin had lower HbA1c levels compared with the participants who took the placebo with insulin. The participants who took 10 mg of dapagliflozin with insulin had lower HbA1c levels compared with the participants who took 5 mg of dapagliflozin with insulin.

The researchers compared the HbA1c levels from the start of the study to the HbA1c levels after 24 and 52 weeks of treatment.

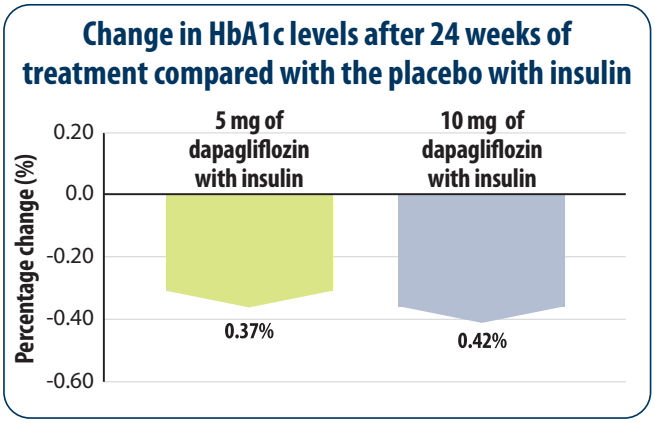
The researchers learned that on average, after 24 weeks of treatment:

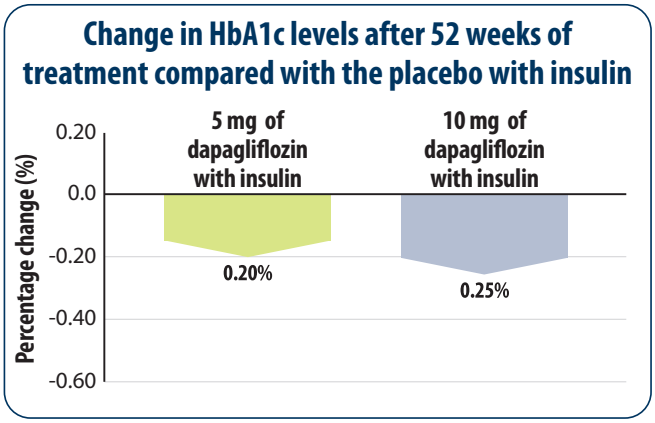
- the participants who took 5 mg of dapagliflozin with insulin had a 0.37% decrease in their HbA1c levels compared with participants who took the placebo with insulin
- the participants who took 10 mg of dapagliflozin with insulin had a 0.42% decrease in their HbA1c levels compared with participants who took the placebo with insulin

Although the researchers were mainly interested in the participants' HbA1c levels after 24 weeks of treatment, they kept measuring the participants' HbA1c levels through 52 weeks of treatment. The researchers learned that on average, after 52 weeks of treatment:

- the participants who took 5 mg of dapagliflozin with insulin had a 0.20% decrease in their HbA1c levels compared with participants who took the placebo with insulin
- the participants who took 10 mg of dapagliflozin with insulin had a 0.25% decrease in their HbA1c levels compared with participants who took the placebo with insulin

The charts below show these results.





What medical problems did the participants have during the study?

This section is a summary of the medical problems the participants had during the study that the doctors thought might be related to the study drug. These medical problems are called "adverse reactions". An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care.

These adverse reactions may or may not be caused by the study drug. A lot of research is needed to know whether a drug causes an adverse reaction. The websites listed at the end of this summary may have more information about the adverse reactions or other medical problems that happened during this study.

How many participants had serious adverse reactions?

There were 3.2% of participants who had serious adverse reactions during the whole 52 weeks of the study. This was 26 out of 813 participants. Participants who took 5 mg of dapagliflozin with insulin had more serious adverse reactions than participants who took 10 mg of dapagliflozin with insulin. Participants who took 10 mg of dapagliflozin with insulin had a similar number of serious adverse reactions as participants who took the placebo with insulin.

The most common serious adverse reaction during the study was increased blood acids due to diabetes called diabetic ketoacidosis, also called DKA. This happened in 1.8% of participants. This was 15 out of 813 participants. Participants who took 5 mg of dapagliflozin with insulin had a similar number of events of DKA as participants who took 10 mg of dapagliflozin with insulin.

One participant died during the study. This death was not related to the study drug.

How many participants had adverse reactions?

There were 27.1% of participants who had adverse reactions during the whole 52 weeks of the study. This was 220 out of 813 participants.

Participants who took 5 mg of dapagliflozin with insulin had a similar number of adverse reactions as participants who took 10 mg of dapagliflozin with insulin. Participants who took dapagliflozin with insulin had more adverse reactions than participants who took the placebo with insulin.

What adverse reactions did the participants have?

In this study, the most common adverse reaction was frequent urination during the daytime. This adverse reaction happened more in participants who took 5 mg of dapagliflozin with insulin than in participants who took 10 mg of dapagliflozin with insulin. This adverse reaction happened more in participants who took dapagliflozin with insulin than in participants who took the placebo with insulin.

The table below shows the most common adverse reactions that happened in at least 2% of participants in any treatment group during the whole 52 weeks of the study. There were other adverse reactions, but these happened in fewer participants.

Most common adverse reactions during the study

	5 mg of dapagliflozin with insulin (out of 271 participants)	10 mg of dapagliflozin with insulin (out of 270 participants)	Placebo with insulin (out of 272 participants)
Frequent urination during the daytime	7.7% (21)	4.8% (13)	2.6% (7)
Increased blood acids due to diabetes	3.0% (8)	2.2% (6)	0.4% (1)
Urinary tract infection	2.6% (7)	2.2% (6)	3.7% (10)
Genital yeast infection in women	1.8% (5)	3.3% (9)	1.5% (4)
Genital fungal infection	1.8% (5)	2.6% (7)	0.0% (0)
Weight loss	1.8% (5)	2.6% (7)	0.4% (1)
Thirst	1.5% (4)	5.2% (14)	0.7% (2)
Increased amount of urine	1.1% (3)	2.6% (7)	0.4% (1)

How many participants had adverse events?

This section is a summary of medical problems called “adverse events” that participants had during the study. An adverse event is any sign or symptom of a medical problem that participants have. Adverse events are different from adverse reactions because they include any medical problem that happens during the study whether the doctor thought the medical problem was caused by the drug or not.

An adverse event is considered “serious” when it is life-threatening, causes lasting problems, or requires hospital care.

How many participants stopped taking the study drug because of adverse events?

There were 3.4% of participants who stopped taking the study drug during the study because of serious adverse events. This was 28 out of 813 participants.

There were 7.3% of participants who stopped taking the study drug during the study because of adverse events. This was 59 out of 813 participants.

How many participants had adverse events of special interest?

The researchers also wanted to find out if participants had specific medical problems called “adverse events of special interest”. An adverse event of special interest is an adverse event that is meaningful for a specific study drug or condition. It may or may not be related to the study drug or condition, but the researchers give it special attention.

In this study, the researchers wanted to find out in particular about 2 adverse events of special interest. These were severe low blood sugar levels and increased levels of acid in the blood.

Severe low blood sugar levels

People with type 1 diabetes can have episodes where their blood sugar levels get too low, also called hypoglycemia. Severe hypoglycemia are episodes of low blood sugar levels that make a person sick enough that they need someone to help them raise their blood sugar level.

In this study, the doctors kept track of how many times participants had severe hypoglycemia. These episodes were counted whether or not the doctors thought they might be related to the study drug.

Overall, during the study, the number of participants who had episodes of severe hypoglycemia was similar between participants who took 5 mg of dapagliflozin with insulin and participants who took 10 mg of dapagliflozin with insulin.

Episodes of severe hypoglycemia during the study			
	5 mg of dapagliflozin with insulin (out of 271 participants)	**10 mg of dapagliflozin with insulin (out of 270 participants)**	**Placebo with insulin (out of 272 participants)**
Participants who had 1 episode	6.6% (18)	4.8% (13)	4.4% (12%)
Participants who had 2 episodes	1.1% (3)	1.9% (5)	1.5% (4)
Participants who had more than 3 episodes	1.1% (3)	3.0% (8)	2.6% (7)

Increased levels of acid in the blood

People with type 1 diabetes can have episodes where they have increased levels of acids in their blood from breaking down fats. This happens when the body's cells are not getting enough sugar, which is often caused by someone taking too little insulin or missing doses of insulin. These acids are called ketones.

When patients have greatly increased levels of ketones in the blood, this is called DKA.

In this study, the doctors kept track of how many participants had DKA and how many times this happened. These episodes were counted whether or not the doctors thought they might be related to the study drug. The main way that episodes of DKA were looked at in this study was by a process called "adjudication".

Adjudication means that expert doctors who were not treating the participants and who did not know whether the participants were getting the study drug or placebo decided what type of event the participant had. They decided whether the event was a definite DKA, possible DKA, or unlikely to be DKA. Only definite events of DKA were thought to be true events of DKA in this study. To make their decision, the doctors looked at many types of information. These included the participants' blood sugar and ketones, symptoms, laboratory results and the report from the participant's doctor.

Overall, during the study, there were more episodes that were adjudicated as a definite DKA in participants who took either dose of dapagliflozin.

Participants with episodes of adjudicated DKA during the study

	5 mg of dapagliflozin with insulin (out of 271 participants)	10 mg of dapagliflozin with insulin (out of 270 participants)	Placebo with insulin (out of 272 participants)
Participants with an event adjudicated as definite DKA	4.1% (11)	3.7% (10)	0.4% (1)
Participants with an event adjudicated as possible DKA	3.0% (8)	1.5% (4)	0.7% (2)
Participants with an event adjudicated as unlikely to be DKA	3.7% (10)	3.7% (10)	3.3% (9)

How has this study helped patients and researchers?

These results helped researchers learn more about how dapagliflozin affects HbA1c levels in people with type 1 diabetes.

Researchers look at the results of many studies to decide which treatments work best and are safest. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with dapagliflozin and insulin taken together are planned.

Where can I learn more about this study?

You can find more information about this study on the websites listed below. If a full report of the study results is available, it can also be found here.

- www.clinicaltrials.gov. Once you are on the website, type **"NCT02460978"** into the search box and click **"Search"**.
- www.clinicaltrialsregister.eu. Once you are on the website, click **"Home and Search"**, then type **"2014-004599-49"** in the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D1695C00007"** into the search box and click **"Find a Study"**.

Full Trial Title: A Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus

AstraZeneca Protocol Number: D1695C00007

AstraZeneca sponsored this study and has its headquarters at 1800 Concord Pike in Wilmington, Delaware.

The phone number for the AstraZeneca Information Center is +1-877-240-9479.

Thank you!

Clinical study participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical studies, nor is it involved in conducting clinical studies.

CISCRP
One Liberty Square, Suite 1100 • Boston, MA 02109
1-877-MED-HERO • www.ciscrp.org