Clinical Study Results

Research Sponsor: AstraZeneca AB

Drugs Studied: Dapagliflozin and metformin

Study Title: A study to learn if the same amount of dapagliflozin/metformin gets into the blood when the tablets are made in the mainland United States or in Puerto Rico

Thank you!

Thank you to the participants who took part in the clinical trial for the study drugs dapagliflozin and metformin. AstraZeneca AB sponsored this study and thinks it is important to share the results. An independent non-profit organization called CISCRP helped prepare this summary of the study results for you.

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?

The study started in January 2018 and ended in January 2019. The sponsor reviewed the data collected when the study ended and created a report of the results. This is a summary of that report.

The study included 288 participants in Brazil.

Why was the research needed?

Researchers want to know if a drug works in the same way when it is made in a factory in the mainland United States as when it is made in a factory in Puerto Rico. This is because the company that makes the drug wants to move its manufacturing process for this drug from Puerto Rico to the mainland United States. Before some drugs can be made in a new location, researchers need to do clinical studies to find out if the drug can be made in the same way. The drug that was tested in this study is to treat type 2 diabetes.

In people with type 2 diabetes, the body does not make enough insulin. Insulin is made by the pancreas and controls the levels of sugar in the blood. If a person's blood sugar levels become too high, he or she can have medical problems.

The study drugs, dapagliflozin and metformin, were designed to help lower the amount of sugar in the blood. Dapagliflozin does this by helping the body remove sugar through urine. Metformin does this by lowering the amount of sugar made by the liver. In this study, the study drugs were taken together in a dapagliflozin/metformin tablet. The researchers wanted to find out if the same amount of a version of dapagliflozin/metformin tablets made in the mainland United States got into the participants' blood as a version made in Puerto Rico.

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

- Did the same amounts of drugs from the dapagliflozin/metformin tablets made in the mainland United States get into participants' blood as the tablets made in Puerto Rico?
- What medical problems did the participants have during the study?

The researchers asked for the help of healthy men and women. Everyone in the study was 18 to 50 years old when they joined.

What kind of study was this?

This was an "open-label" study. This means that the researchers and the participant knew what the participant was taking.

This study had 4 parts. Each participant was only in 1 of these parts. In each part, 72 participants took dapagliflozin/metformin tablets. Doses were measured in milligrams, also called mg.

In Parts 1 and 2, the participants took tablets that had 5 mg of dapagliflozin and 500 mg of metformin. These tablets are called 5/500 mg tablets.

In Parts 3 and 4, the participants took tablets that had 10 mg of dapagliflozin and 1,000 mg of metformin. These tablets are called 10/1,000 mg tablets.

In each part, the participants took 1 tablet that was made in the mainland United States, and 1 tablet that was made in Puerto Rico. But the participants took these in a different order.

In Parts 1 and 3, the participants took the tablets with food. In Parts 2 and 4, they took the tablets without food.

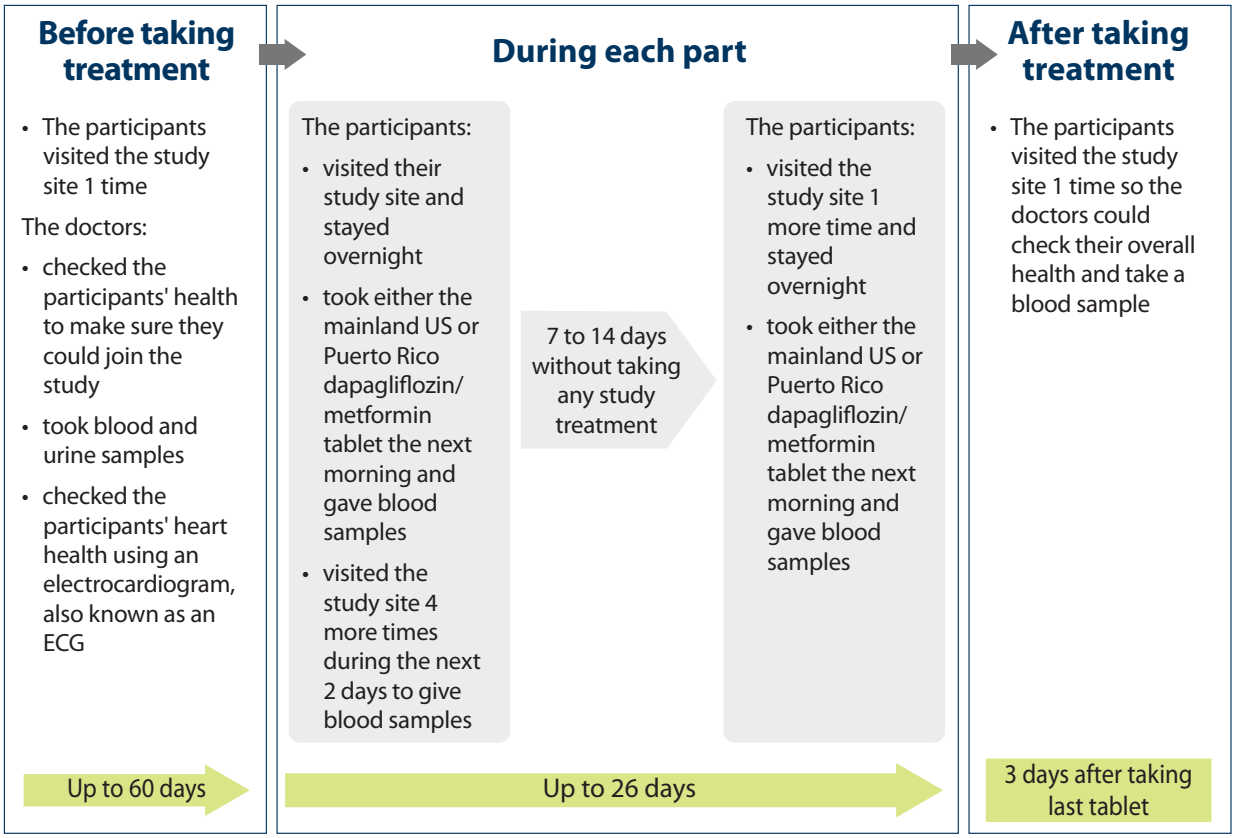
The table below shows a summary of the different parts.

Part	Amount of drug	With or without food
1	5/500 mg	With food
2	5/500 mg	Without food
3	10/1,000 mg	With food
4	10/1,000 mg	Without food

A computer program was used to randomly choose the order that each participant took the treatments. 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?

The figure below shows what happened during the study.



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.

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 change.

The websites listed at the end of this summary may have a full report of the study results.

There were some participants who left the study early and did not finish treatment. So, they either took only the tablet made in the United States, or only the tablet made in Puerto Rico. The number of participants who completed each part and took both tablets was:

- 51 participants in Part 1
- 51 participants in Part 2
- 49 participants in Part 3
- 41 participants in Part 4

Because 96 participants left the study early, the results below include information for the remaining 192 participants.

Did similar amounts of drugs from the dapagliflozin/metformin tablets made in the mainland United States get into participants' blood as the tablets made in Puerto Rico?

Yes. The researchers found that overall, the same amount of drugs from the dapagliflozin/metformin tablets made in the mainland United States got into the participants' blood as the tablets made in Puerto Rico.

To answer this question, the doctors measured the levels of dapagliflozin and of metformin in the participants' blood. They measured the highest amount of each drug in the blood of each participant. They also measured the total amount of each drug in the blood of each participant. The researchers then calculated the average highest and average total amounts of dapagliflozin and metformin in the blood for each group.

Once the researchers found the averages in each part of the study, they compared:

- the average highest amount of dapagliflozin in the blood after taking tablets made in the mainland United States with those made in Puerto Rico
- the average highest amount of metformin in the blood after taking tablets made in the mainland United States with those made in Puerto Rico
- the average total amount of dapagliflozin in the blood after taking tablets made in the mainland United States with those made in Puerto Rico
- the average total amount of metformin in the blood after taking tablets made in the mainland United States with those made in Puerto Rico

They compared the averages as a percentage. They did this for each part of the study.

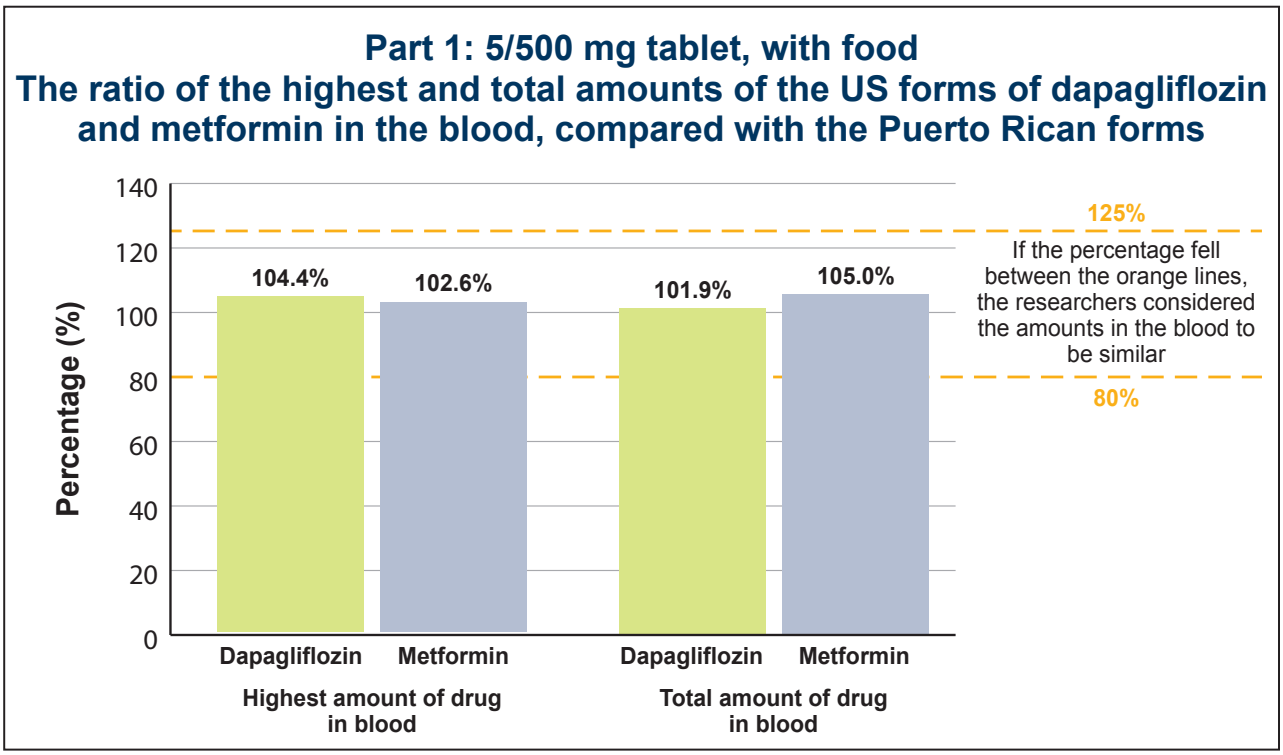
If the percentage was between 80% and 125%, the researchers considered the amounts of dapagliflozin or metformin in the blood to be the similar. A percentage higher than 100% meant that there was more of the drug from the tablet made in the mainland United States in the blood. A percentage lower than 100% meant that there was more of the drug from the tablet made in Puerto Rico in the blood.

Part 1

When comparing the tablets made in Puerto Rico to the tablets made in the mainland United States, the researchers found the following percentages.

- The average highest amount of drug found in the blood was:
  - 104.4% for dapagliflozin
  - 102.6% for metformin
- The average total amount of drug found in the blood was:
  - 101.9% for dapagliflozin
  - 105.0% for metformin

The chart below shows these results.

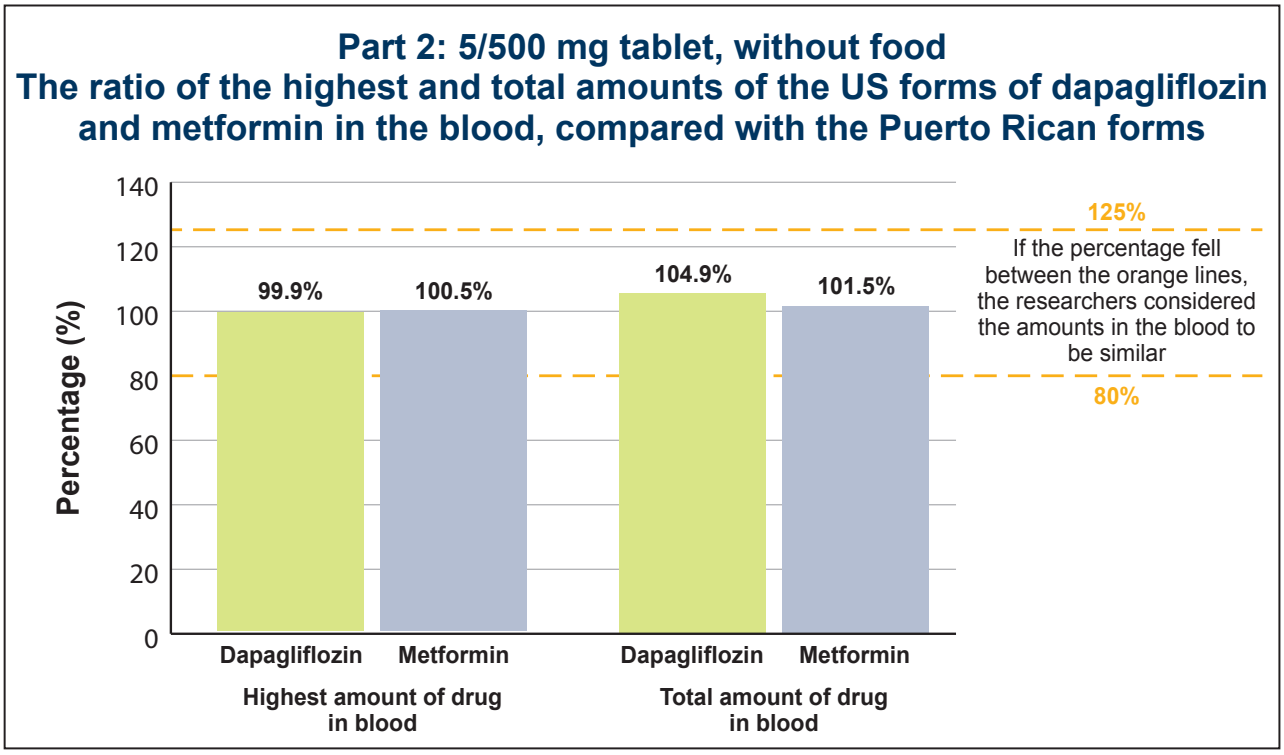


Part 2

When comparing the tablets made in Puerto Rico to the tablets made in the mainland United States, the researchers found the following percentages.

- The average highest amount of drug found in the blood was:
  - 99.9% for dapagliflozin
  - 100.5% for metformin
- The average total amount of drug found in the blood was:
  - 104.9% for dapagliflozin
  - 101.5% for metformin

The chart below shows these results.

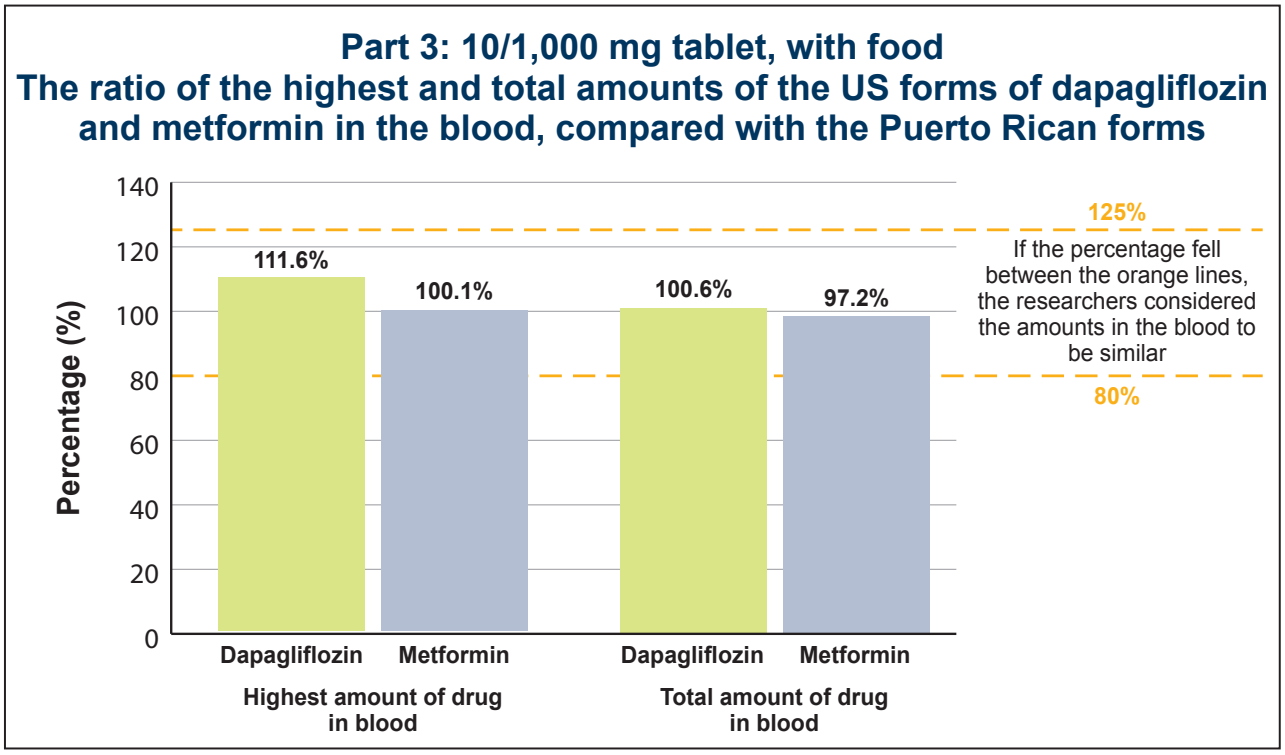


Part 3

When comparing the tablets made in Puerto Rico to the tablets made in the mainland United States, the researchers found the following percentages.

- The average highest amount of drug found in the blood was:
  - 111.6% for dapagliflozin
  - 100.1% for metformin
- The average total amount of drug found in the blood was:
  - 100.6% for dapagliflozin
  - 97.2% for metformin

The chart below shows these results.

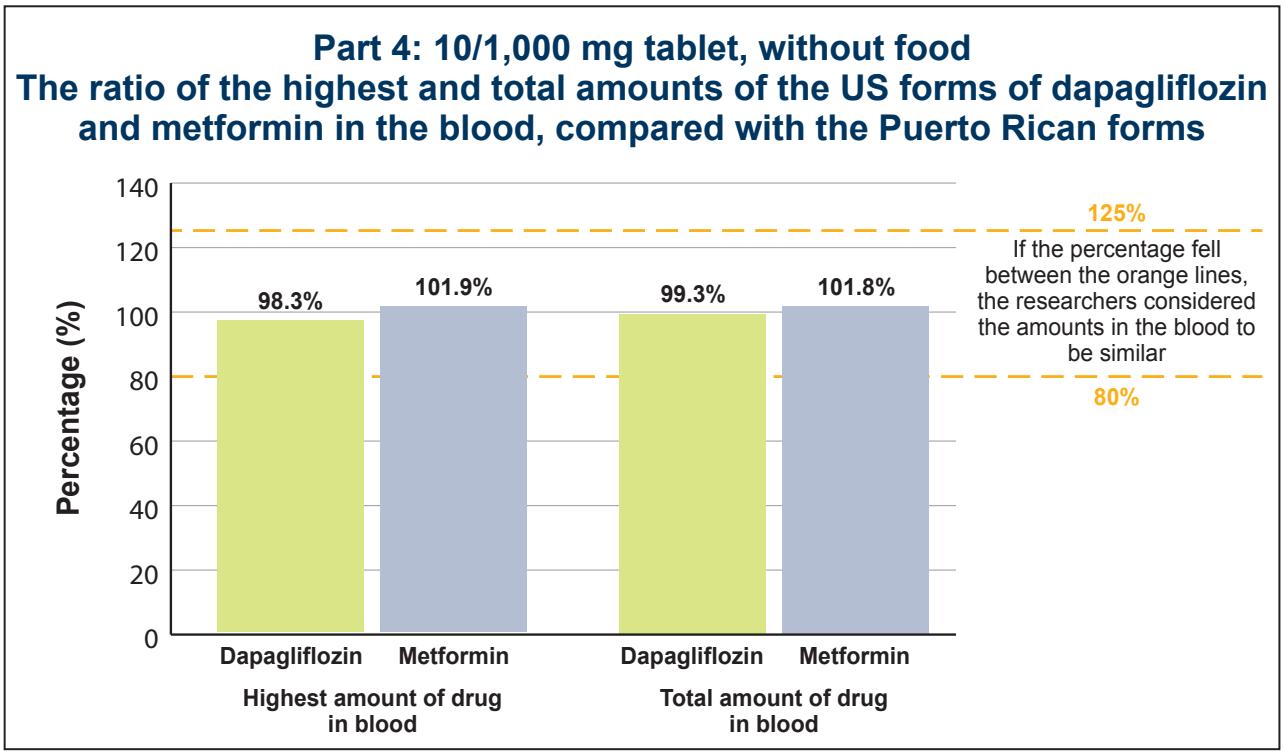


Part 4

When comparing the tablets made in Puerto Rico to the tablets made in the mainland United States, the researchers found the following percentages.

- The average highest amount of drug found in the blood was:
  - 98.3% for dapagliflozin
  - 101.9% for metformin
- The average total amount of drug found in the blood was:
  - 99.3% for dapagliflozin
  - 101.8% for metformin

The chart below shows these results.



What medical problems did participants have during the study?

This section is a summary of the medical problems the participants had during the study that the study 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 drugs. 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 other information about adverse reactions or other medical problems that happened during this study.

The results below include all 288 participants, because each participant took at least 1 dapagliflozin/metformin tablet.

How many participants had serious adverse reactions?

None of the participants had serious adverse reactions during this study.

How many participants had adverse reactions?

- 41.6% of participants had adverse reactions during Part 1 of the study. This was 30 out of 72 participants.
- 30.5% of participants had adverse reactions during Part 2 of the study. This was 22 out of 72 participants.
- 48.6% of participants had adverse reactions during Part 3 of the study. This was 35 out of 72 participants.
- 55.5% of participants had adverse reactions during Part 4 of the study. This was 40 out of 72 participants.

None of the participants stopped taking study treatment because of adverse reactions they had during the study.

What adverse reactions did the participants have?

The most common adverse reaction was having white blood cells in urine.

The table below shows the adverse reactions that happened during the study. Some participants had more than 1 adverse reaction.

Adverse reactions during the study

	Part 1 5/500 mg tablet out of 72 participants	Part 2 5/500 mg tablet out of 72 participants	Part 3 10/1,000 mg tablet out of 72 participants	Part 4 10/1,000 mg tablet out of 72 participants
White blood cells in urine	30.5% (22)	18.1% (13)	25.0% (18)	38.9 (28)
Decreased kidney function	8.3% (6)	4.2% (3)	13.8% (10)	5.6% (4)
Low levels of blood sugar	4.2% (3)	0.0% (0)	0.0% (0)	0.0% (0)
Headache	1.4% (1)	6.9% (5)	4.2% (3)	4.2% (3)
Yeast infection	1.4% (1)	0.0% (0)	0.0% (0)	2.8% (2)
Urinary tract infection	1.4% (1)	0.0% (0)	0.0% (0)	1.4% (1)
Diarrhea	0.0% (0)	1.4% (1)	5.6% (4)	2.8% (2)
Vomiting	0.0% (0)	0.0% (0)	4.2% (3)	1.4% (1)
Protein in urine	0.0% (0)	0.0% (0)	8.3% (6)	0.0% (0)
Blood in urine	0.0% (0)	1.4% (1)	0.0% (0)	0.0% (0)
High cholesterol	0.0% (0)	2.8% (2)	0.0% (0)	1.4% (1)
Skin rash	0.0% (0)	1.4% (1)	0.0% (0)	0.0% (0)
Allergic reaction	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)
Hives	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)
Stomach pain	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)
Nausea	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)
Flu	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)

How has this study helped patients and researchers?

This study helped researchers learn if dapagliflozin/metformin tablets made in the mainland United States and in Puerto Rico acted the same way in the blood of healthy participants.

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/metformin tablets are not planned.

Where can I learn more about this study?

More information about this study is available on the website 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 this website, type **"NCT03216278"** into the search box, and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D1691C00016"** into the search box, and click **"Find a Study"**.

Full Trial Title: A four-part bioequivalence study to compare two fixed-dose combination (FDC) tablets of dapagliflozin/metformin XR 5/500 mg (Part 1 and 2) and 10/1000 mg (Part 3 and 4) manufactured at two different plants (Humacao, Puerto Rico and Mount Vernon, US) in healthy subjects under fasting and fed conditions

National Clinical Trials number: NCT03216278

AstraZeneca Protocol Number: D1691C00016

AstraZeneca AB sponsored this study and has its headquarters in Södertälje, Sweden.

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 participants.

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