

EMPA-REG OUTCOME[®] Trial

Background

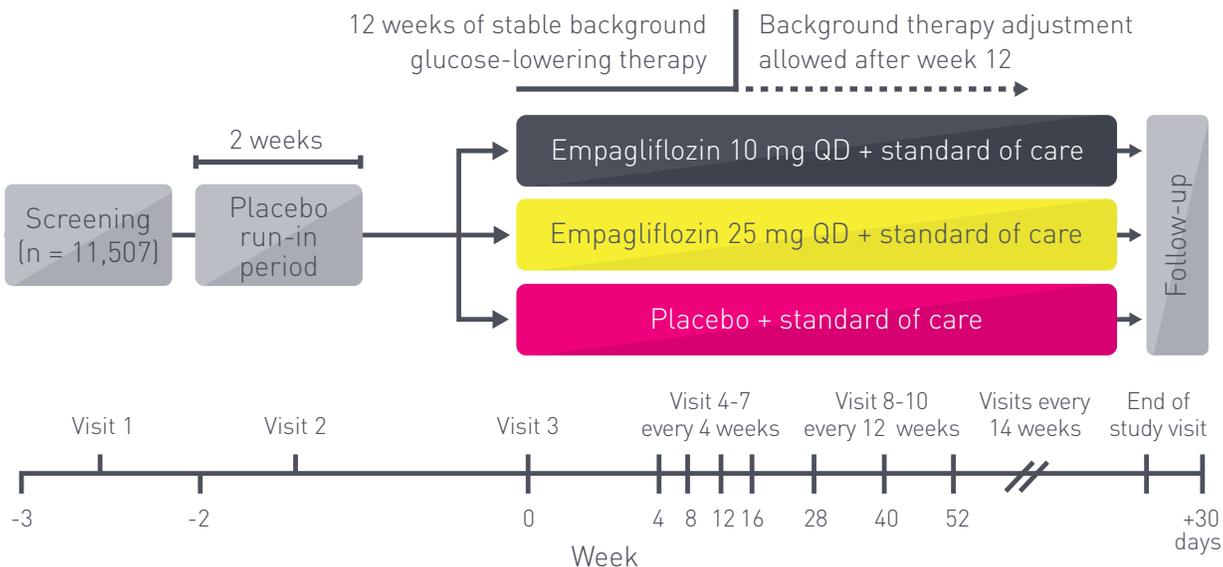
Introduction

About 415 million people worldwide have diabetes — a chronic condition that occurs when the body does not properly produce or use the hormone insulin.¹ In the U.S., about 29 million Americans, including approximately 12 percent of the population aged 20 and older, have diabetes. Type 2 diabetes (T2D) is the most common type of diabetes, accounting for an estimated 90 to 95 percent of all diagnosed adult diabetes cases in the U.S.²

Due to the complications associated with diabetes, such as high blood sugar, high blood pressure and obesity, cardiovascular disease (CVD) is a major complication and the leading cause of death associated with diabetes.^{3,4} People with diabetes are two to four times more likely to develop CVD than people without diabetes.³ Approximately two out of three people with T2D die from CVD.⁵

Given the association between CVD and diabetes, studies to determine the long-term effects of diabetes treatments on cardiovascular (CV) outcomes are important. The EMPA-REG OUTCOME[®] trial was a long-term, multicenter, randomized, double-blind, placebo-controlled trial that investigated CV outcomes for Jardiance[®] (empagliflozin) tablets in more than 7,000 patients, from 42 countries, with T2D and established CVD.⁶

Trial Design⁶



The study was designed to assess the effect of JARDIANCE (10 mg or 25 mg once daily) on CV events. JARDIANCE was added to standard of care and compared with placebo plus standard of care in patients with T2D and established CVD. The study was designed to first test for non-inferiority and then for superiority.

Standard of care was comprised of glucose-lowering agents and CV drugs (including for blood pressure and cholesterol).

Primary endpoint:

Time to first occurrence of either CV death, non-fatal heart attack (myocardial infarction) or non-fatal stroke

Key inclusion criteria:

- High risk of CV events due to previous CV event or established CVD
- Insufficient glycemic control

For more information on the EMPA-REG OUTCOME trial, visit clinicaltrials.gov (Identifier: NCT01131676)

Results Summary

Over a median of 3.1 years:

- JARDIANCE significantly reduced the risk of the combined primary endpoint of CV death, non-fatal heart attack or non-fatal stroke by 14 percent versus placebo (HR 0.86, 95% CI: 0.74-0.99); absolute risk reduction was 1.6 percent for JARDIANCE versus placebo.⁶
- Risk of CV death was significantly reduced by 38 percent (HR 0.62, 95% CI: 0.49-0.77); absolute risk reduction was 2.2 percent for patients taking JARDIANCE versus placebo. There was no change in the risk of non-fatal heart attack (HR 0.87, 95% CI: 0.70-1.09) or non-fatal stroke (HR 1.24, 95% CI: 0.92-1.67).⁶

JARDIANCE is not for people with type 1 diabetes or people with diabetic ketoacidosis (increased ketones in the blood or urine). Adults with T2D should not take JARDIANCE if they have severe kidney problems or are on dialysis, or if they are allergic to empagliflozin or any ingredient in JARDIANCE. JARDIANCE can cause dehydration and low blood pressure. JARDIANCE can also cause increased ketones in the blood (ketoacidosis), serious urinary tract infection, acute kidney injury and impairment in renal function, low blood glucose when used with insulin or insulin secretagogues (e.g. sulfonylurea, a medication used to treat T2D), vaginal yeast infections and yeast infections of the penis, and increased cholesterol.⁷

What is JARDIANCE? (www.jardiance.com/)

JARDIANCE is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

JARDIANCE reduces the risk of cardiovascular death in adults with type 2 diabetes who have known cardiovascular disease.

JARDIANCE is not for people with type 1 diabetes or for people with diabetic ketoacidosis (increased ketones in the blood or urine).

Important Safety Information

What is the most important information I should know about JARDIANCE?

JARDIANCE can cause serious side effects, including:

- **Dehydration.** JARDIANCE can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up.

You may be at a higher risk of dehydration if you:

- have low blood pressure
 - take medicines to lower your blood pressure, including water pills (diuretics)
 - are on a low salt diet
 - have kidney problems
 - are 65 years of age or older.
- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis is a serious condition and may need to be treated in the hospital. Ketoacidosis may lead to death. Ketoacidosis occurs in people with type 1 diabetes and can also occur in people with type 2 diabetes taking JARDIANCE, even if blood sugar is less than 250 mg/dL. **Stop taking JARDIANCE and call your doctor right away if you get any of the following symptoms**, and if possible, check for ketones in your urine:
 - nausea
 - vomiting
 - stomach-area (abdominal) pain
 - tiredness
 - trouble breathing
 - **Serious urinary tract infections.** Serious urinary tract infections can occur in people taking JARDIANCE and may lead to hospitalization. Tell your doctor if you have symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often or right away, pain in the lower part of your stomach or pelvis, or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
 - **Vaginal yeast infection.** Women who take JARDIANCE may get vaginal yeast infections. Talk to your doctor if you experience vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), and/or vaginal itching.
 - **Yeast infection of the penis.** Men who take JARDIANCE may get a yeast infection of the skin around the penis, especially uncircumcised males and those with chronic infections. Talk to your doctor if you experience redness, itching or swelling of the penis, rash of the penis, foul smelling discharge from the penis, and /or pain in the skin around penis.

Who should not take JARDIANCE?

Do not take JARDIANCE if you are allergic to empagliflozin or any of the ingredients in JARDIANCE. Symptoms of serious allergic reactions to JARDIANCE may include:

- skin rash
- raised red patches on your skin (hives)
- swelling of the face, lips, tongue, and throat that may cause difficulty breathing or swallowing.

If you have any of these symptoms, stop taking JARDIANCE and contact your doctor or go to the nearest emergency room right away.

Do not take JARDIANCE if you have severe kidney problems or are on dialysis.

What should I tell my doctor before using JARDIANCE?

Tell your doctor if you:

- have kidney problems. Your doctor may do blood tests to check your kidneys before and during your treatment with JARDIANCE
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery
- are eating less due to illness, surgery, or a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term (“binge” drinking)
- have any other medical conditions
- are pregnant or planning to become pregnant. It is unknown if JARDIANCE will harm your unborn baby
- are breastfeeding, or plan to breastfeed. It is unknown if JARDIANCE passes into your breast milk.

Tell your doctor about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take water pills (diuretics) or medicines that can lower your blood sugar such as insulin.

What are other possible side effects of JARDIANCE?

- **Low blood sugar** (hypoglycemia): if you take JARDIANCE with another medicine that can cause low blood sugar, such as sulfonylurea or insulin, your risk of low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered. Symptoms of low blood sugar may include:
 - Headache
 - Drowsiness
 - Weakness
 - Dizziness
 - Confusion
 - Irritability
 - Hunger
 - Fast heart beat
 - Sweating
 - Shaking or feeling jittery

- **Kidney Problems**, Sudden kidney injury has happened in people taking JARDIANCE. Talk to your doctor right away if you reduce the amount you eat or drink, or if you lose liquids; for example, from vomiting, diarrhea, or being in the sun too long.
- **Increased fats in your blood (cholesterol).**

The most common side effects of JARDIANCE include urinary tract infections, and yeast infections in females.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For more information, please see [full Prescribing Information](#) and [Patient Information](#).

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7. Jardiance® (empagliflozin) tablets U.S. Prescribing Information.