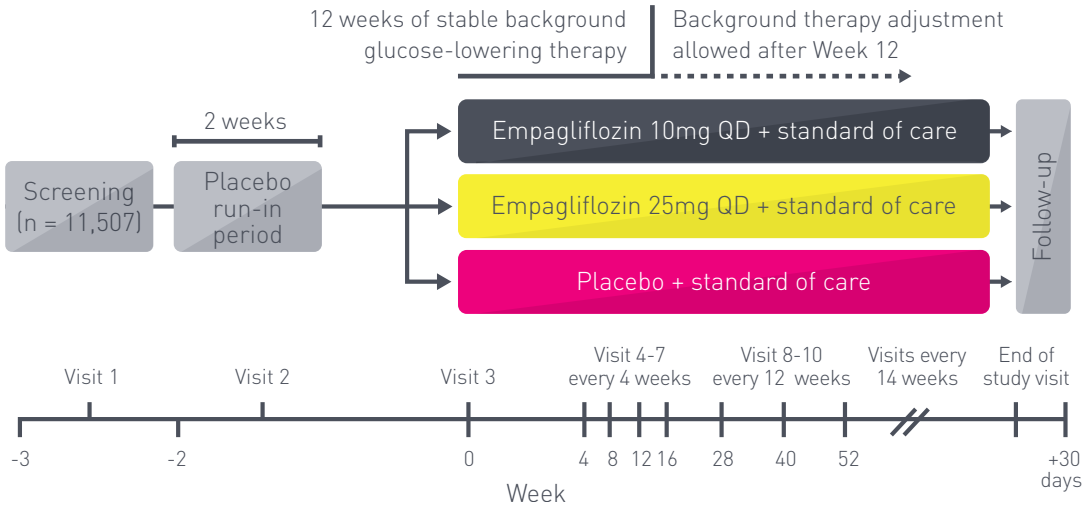
EMPA-REG OUTCOME®
Trial Design Backgrounder

Introduction

Approximately 50 percent of people with type 2 diabetes (T2D) worldwide die due to cardiovascular disease (CVD), making it the leading cause of death in this population.[1,2] The relationship between diabetes and CVD is complex. Diabetes is a risk factor for CVD. Additionally, conditions such as high blood pressure and obesity, which are more common in people with diabetes, are also risk factors for CVD.[1]

Given the association between CVD and diabetes, studies to establish the CV safety profile of diabetes treatments are highly important. The EMPA-REG OUTCOME® trial was a long-term clinical trial which investigated CV outcomes for Jardiance® (empagliflozin) in more than 7,000 adults with T2D at high risk for CV events.

Trial design[3]



EMPA-REG OUTCOME® was a multicenter, randomized, double-blind, placebo-controlled trial.[4] The study was designed to assess the effect of JARDIANCE (empagliflozin) (10mg or 25mg once daily) on CV events. JARDIANCE was added to standard of care and compared with placebo in adults with T2D at high risk of CV events. The study was designed to first test for non-inferiority and then for superiority.

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Standard of care comprised glucose lowering agents and CV drugs (including antihypertensive and lipid lowering agents).

Primary endpoint:

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

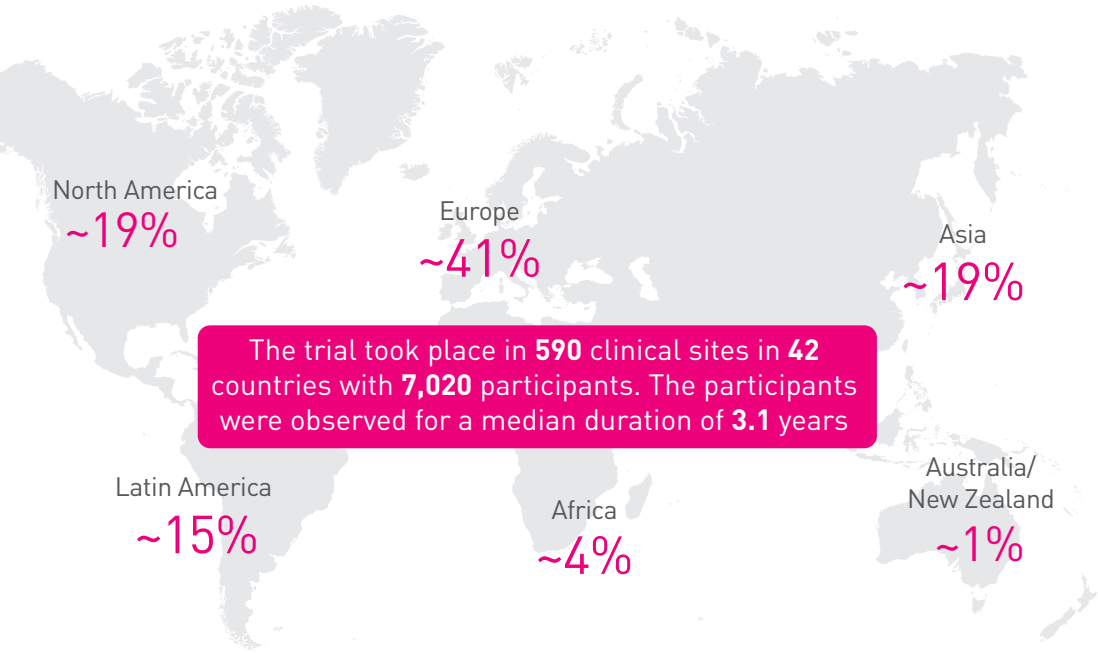
Key secondary endpoints:

Time to first occurrence of either CVD, non-fatal heart attack (myocardial infarction), non-fatal stroke or hospitalization for unstable angina pectoris (chest pain due to coronary heart disease leading to hospitalization)

Key inclusion criteria:

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

Study Population



The trial took place in **590** clinical sites in **42** countries with **7,020** participants. The participants were observed for a median duration of **3.1** years

Glucose Lowering Therapy at Baseline

2% of participants were drug-naïve
29% were receiving monotherapy
45% were receiving dual therapy
36% were using insulin as monotherapy or part of dual therapy

CV drugs at baseline:

77% of patients were receiving a statin
9% were receiving a fibrate
85% were being treated with an acetylsalicylic acid agent
94% were receiving any drug for BP reduction (**80%** on blockers of the renin-angiotensin system)

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.
- **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
- 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.

Important Safety Information (continued)

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
  - Confusion
  - Sweating
  - Drowsiness
  - Irritability
  - Shaking or feeling jittery
  - Weakness
  - Hunger
  - Dizziness
  - Fast heart beat
- **Kidney Problems**, especially in people 75 years of age or older and people who already have kidney problems
- **Urinary Tract Infection:** symptoms may include burning feeling when passing urine, pain in the pelvis or back, or urine that looks cloudy
- **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, including Patient Information.

JARCONSISI 8.1.2014

References

1. World Heart Federation. Diabetes as a risk factor for cardiovascular disease. Available from: http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/diabetes/ (accessed: January 2015).

2. Organization WH. Diabetes: fact sheet no. 312. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/# (updated October 2013; accessed: January 2014).

3. Zinman B, *et al*. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol.* 2014;**13**:102.

4. ClinicalTrials.Gov. BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). Available from: https://clinicaltrials.gov/ct2/show/NCT01131676 (accessed: Jan 2015).

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