Dear Reader,

Pharmaceutical companies (sponsors) plan and conduct clinical studies to test medicines. Afterwards, they write study reports. A study report describes how a study was done and what the results of the study were. This is a summary of such a report. It is meant for the general reader. Complex medical explanations have been avoided as much as possible. The sponsor for this study was Boehringer Ingelheim.

You may be interested in this summary because you want to learn about treatment options for diabetes. This summary describes the results of a single study. The results may not apply to everybody.

This study started in August 2010 and finished in August 2015. This summary includes the main results of the study based on information collected up to September 2013. The study was still ongoing at the time. The full results of the completed study will be provided in a later summary. The lay title for this study is 'Efficacy and Safety of Empagliflozin (BI 10773) with Metformin in Patients with Type 2 Diabetes'.

What was the study about?

This study compared 2 medicines to treat patients with type 2 diabetes. Researchers wanted to see how well the medicines worked when taken for a long period of time. They also wanted to know what side effects there were, and how well patients tolerated the medicines. Patients in this study were already taking a common diabetes medicine called metformin. Metformin alone did not control their diabetes well. During this study, patients continued to take metformin. They also took 1 of the study medicines for 2 years: either a medicine called empagliflozin, or a medicine called glimepiride. Some patients continued to take study medicine for up to 2 additional years in an extension period of the study.

Why was the research needed?

Patients with type 2 diabetes have too much sugar (glucose) in their blood. This can increase the risk of medical problems such as heart or kidney disease. Therefore, controlling blood sugar is important for patients with type 2 diabetes.

Patients may be able to control their blood sugar by following a diet and exercise plan. Sometimes, medicine may be needed as well. Metformin is often the first medicine used. If metformin alone does not control the blood sugar, additional medicines may be needed. There is a need to develop medicines that allow patients to control their blood sugar over long periods of time with fewer side effects.

This study tested whether taking empagliflozin or glimepiride, in addition to metformin, improved control of blood sugar.

Which medicines were studied?

The researchers compared 2 medicines that lower blood sugar. These were:

- **Empagliflozin:** a new medicine to treat type 2 diabetes. It works by blocking a protein called SGLT-2 in the kidneys. Empagliflozin helps the kidneys filter sugar out of the blood and into urine (pee). Urinating (peeing) more sugar out of the body lowers blood sugar.
- **Glimepiride:** a medicine that has been used for many years to treat type 2 diabetes. It works by helping the body to make more insulin. More insulin in the blood lowers the amount of sugar in the blood.

What did the researchers want to know?

The researchers compared empagliflozin to glimepiride. They measured the amount of a protein called glycated haemoglobin (HbA_{1c}) in the blood. Doctors measure HbA_{1c} levels to see how controlled the blood sugar of a patient has been over the past 3 months. The lower the HbA_{1c} level, the better the blood sugar is controlled.

The researchers measured the amount of HbA_{1c} in the patients' blood at the beginning of the study. Researchers also measured the HbA_{1c} level during the 2 years of treatment. The researchers wanted to know how much the HbA_{1c} level in patients' blood changed after 2 years of treatment with each study medicine. In addition, researchers collected information on the side effects of both medicines.

Who participated in the study?

Patients in this study had type 2 diabetes. They had taken metformin and followed a diet and exercise plan, but still had high blood sugar.

Patients were at least 18 years old. The average age (mean) was 55.9 years old. The youngest patient was 23 years old and the oldest was 83 years old. Patients could be in the study if they had:

- Taken only metformin and no other medications for their diabetes for at least the last 3 months
- An HbA_{1c} level from 7.0% to 10.0% at the start of the study
- Followed a diet and an exercise plan

Overall, 1545 patients were treated; 853 were men and 692 were women. The table on the next page lists the regions and countries that took part in the study.

Europe and South Africa (639 patients):

Austria
Czech Republic
Finland
Italy
Netherlands
Norway
Portugal
South Africa
Spain
Sweden
Switzerland
United Kingdom

Asia (434 patients):

Hong Kong
India
Malaysia
Philippines
Taiwan
Thailand

Latin America (276 patients):

Argentina
Colombia
Mexico

North America (196 patients):

Canada
United States

How was this study performed?

Empagliflozin comes in a tablet, and glimepiride comes in a capsule. The study results could be affected if the patient or the study doctor knew which medicine the patient was taking. To prevent this, patients took 1 of the medicines and a placebo each day. The placebo in this study was a tablet or capsule that looked like the other medicines, but contained no active medicine. Neither the patients in the groups nor the study doctors knew which medicines the patients got. This is called a 'double-blind design'.

Patients were divided into 2 groups of similar size. It was decided by chance who got into which group (randomised). The patients in each group took the following medicines each day:

Empagliflozin group: 1 tablet of 25 mg empagliflozin and 1 placebo capsule

Glimepiride group: 1 capsule of glimepiride (1 to 4 mg) and 1 placebo tablet

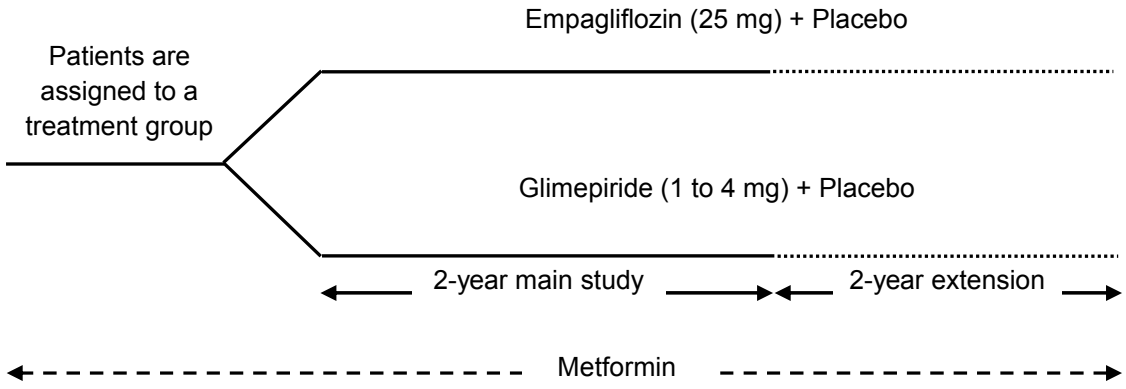
All patients took metformin every day while they were in the study.

Patients could take study medicine for up to 2 years. Some patients continued to take study medicine for another 2 years (the extension period). This summary presents the main results found after the first 2 years of treatment.

Except for taking the different medicines, all patients followed the same procedures:

- Patients went to the study doctor every 4 to 13 weeks.
- Doctors took blood samples at specific visits.
- Doctors collected information on side effects.
- Patients answered questions about their health at specific visits.

The doctors reviewed the blood test results. They also discussed any health problems with the patients and performed further medical tests when needed. The study design is shown in the figure below.



What were the results of this study?

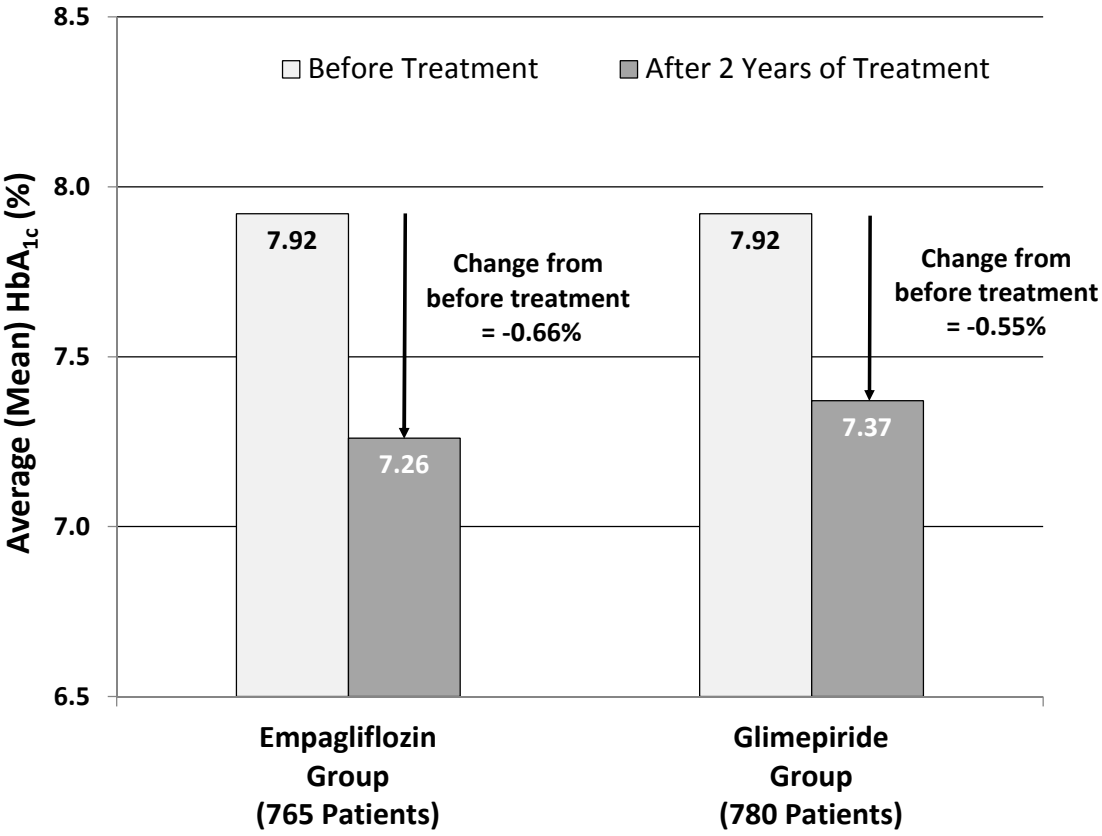
The researchers compared the HbA_{1c} levels of patients who had been treated for 2 years with empagliflozin or glimepiride with the levels at the beginning of the study. Doctors measure HbA_{1c} levels to see how controlled the blood sugar of a patient has been over the past 3 months.

To be sure that the results were reliable, researchers tested whether the results could have come about by chance. This was done by using statistical tests. Some of these statistical tests involved the calculation of so-called p-values. A small p-value (smaller than 0.05) shows that the results are unlikely due to chance. Larger p-values show that the results are possibly due to chance.

Was empagliflozin as good as glimepiride in lowering HbA_{1c}?

Yes. After 2 years of treatment, HbA_{1c} decreased in both groups. HbA_{1c} changed by -0.66% in patients who took empagliflozin. HbA_{1c} changed by -0.55% in patients who took glimepiride. A statistical test was done to see if empagliflozin was at least as good as glimepiride in reducing HbA_{1c}. The results of this test had a p-value of less than 0.0001. This value suggests that the study result was very unlikely due to chance.

The picture on the next page shows the average (mean) level of HbA_{1c} before treatment and after 2 years of treatment for each group. It also shows the change in the HbA_{1c} level from before treatment to the end of 2 years of treatment for each group.



This picture shows the change in HbA$_{1c}$ from before treatment (light bars) to the end of treatment 2 years later (dark bars). HbA$_{1c}$ changed by -0.66% in patients who took empagliflozin over 2 years. HbA$_{1c}$ changed by -0.55% in patients who took glimepiride.

Which side effects did patients have?

A side effect is any medical problem seen during a study. Some side effects are caused by the study medicines, and some side effects are caused by the other medicines taken by the patient. Others are caused by the disease, and some have yet a different cause. Some side effects might happen only once for 1 patient and last for a very short time. Other side effects might happen many times for many patients and last for a long time. Researchers keep track of all medical problems patients have during a study.

Fewer side effects were reported by patients who took empagliflozin during the 2 years of treatment. About 24.8% of patients taking empagliflozin and 32.3% of patients taking glimepiride had at least 1 side effect that their doctor thought was related to the study medicine.

Patients who took empagliflozin were less likely to have low blood sugar (hypoglycaemia)

(19 patients, or 2.5%) related to study medicine than patients who took glimepiride (137 patients, or 17.5%).

The table below shows how many patients had side effects related to study medicine that occurred in at least 2% of patients in either treatment group.

	Empagliflozin (770 patients)	**Glimepiride (783 patients)**
Patients with any side effect related to study medicine	191 patients (24.8%)	253 patients (32.3%)
Low blood sugar (Hypoglycaemia)	19 patients (2.5%)	137 patients (17.5%)
High blood sugar (Hyperglycaemia)	21 patients (2.7%)	26 patients (3.3%)
Urinary tract infection	32 patients (4.2%)	45 patients (5.7%)
Frequent urination or peeing (Pollakiuria)	21 patients (2.7%)	6 patients (0.8%)
Thirst	16 patients (2.1%)	1 patient (0.1%)

Most side effects were mild or moderate in their intensity. Some patients left the study early because of side effects. The proportion of patients who left the study early because of side effects was similar in both groups: 39 patients (5.1%) in the empagliflozin group and 34 patients (4.4%) in the glimepiride group.

In the empagliflozin group, 119 patients (15.6%) had at least 1 serious side effect. In the glimepiride group, 89 patients (11.4%) had at least 1 serious side effect. This means that they had side effects that made them go to the hospital or stay in the hospital. This can also mean that these side effects needed urgent attention by a doctor, were life-threatening, or led to death.

Ten patients died during the first 2 years of the study. Five of these deaths occurred in each treatment group. The study doctors determined that these deaths were not related to the study medicines.

Are there follow-up studies?

No follow-up studies are planned.

Where can I find more information?

The protocol number of the study is 1245.28. The full title of the study is:

'A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment'.

Please visit the following website to find a scientific summary of the study results:

http://trials.boehringer-ingelheim.com/trial_results.html.

You can find more details at www.clinicaltrialsregister.eu by searching for the EudraCT number 2009-016244-39 or at www.clinicaltrials.gov by searching for the NCT number NCT01167881.

Important notice

This summary shows only the results from one study and may not represent all of the knowledge about the medicine studied. Usually, more than one study is carried out in order to find out how well a medicine works and the side effects of the medicine. Other studies may have different results.

You should not change your therapy based on the results of this study without first talking to your treating physician. Always consult your treating physician about your specific therapy.

Boehringer Ingelheim has provided this lay summary in accordance with European Union transparency obligations.