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. 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: either a medicine called empagliflozin, or a medicine called glimepiride. Researchers analysed the results after patients had taken the medicines for 2 years. These results were presented in an earlier summary. Some patients continued to take study medicine for up to 2 additional years in an extension period of the study. This summary presents results for these patients who were in the study for up to 4 years.

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. Patients whose blood sugar is not controlled have high HbA_{1c} levels.

The researchers measured the amount of HbA_{1c} in the patients' blood at the beginning of the study. The main purpose of the study was to learn how much the HbA_{1c} level in patients' blood changed after 2 years of treatment. During the extension period, researchers continued to measure HbA_{1c} levels for an additional 2 years, over a total of 4 years of treatment. They wanted to know if the study medicines would help control patients' blood sugar levels over a longer time. Researchers also collected information on the side effects of both medicines over the 4 years of treatment.

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 had to be 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. After 2 years of treatment, 1075 patients continued treatment for up to an additional 2 years. The table on the next page lists the regions and countries that took part in the study.

Europe and South Africa (639 patients):

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

Asia (434 patients):

Hong Kong	Philippines
India	Taiwan
Malaysia	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

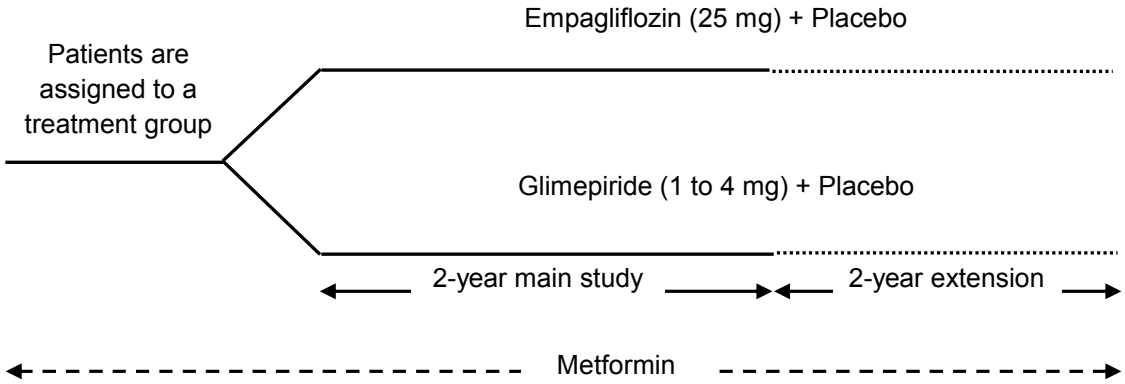
All patients took metformin every day while they were in the study.

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 results found after the first 2 years of treatment and the results found after up to 4 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?

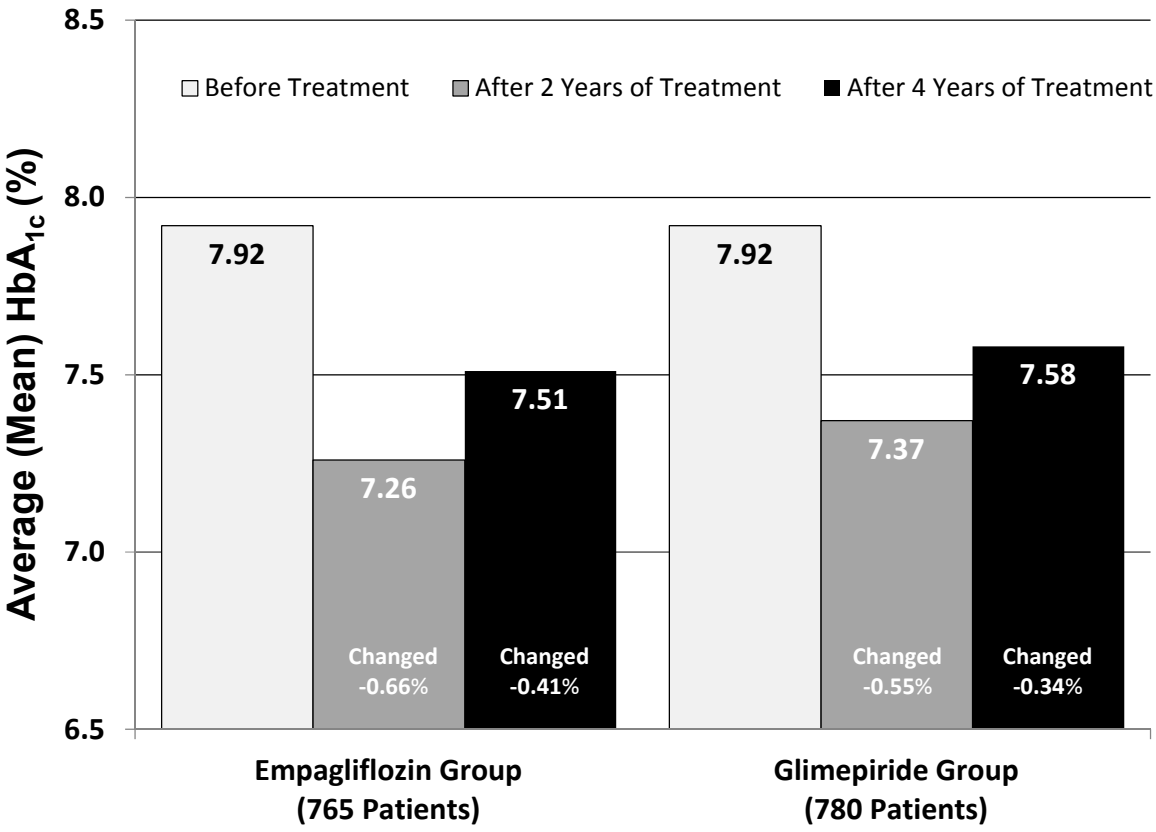
The researchers compared the change in the average HbA_{1c} levels after 2 and 4 years of treatment between the empagliflozin group and the glimepiride group.

As reported in the previous summary, patients in both groups had lower average HbA_{1c} levels after 2 years of treatment. At 2 years, patients who had taken empagliflozin had lower HbA_{1c} levels than patients who had taken glimepiride.

After 4 years of treatment, patients in both groups had lower average HbA_{1c} levels than before they started treatment. The average HbA_{1c} levels were also slightly lower for patients who took empagliflozin than for patients who took glimepiride.

This study was of a long duration, and some patients were not treated with the study medicines for the full 4 years. A total of 515 (67.3%) patients receiving empagliflozin and 462 (59.2%) patients receiving glimepiride were treated with these medicines for the full 4 years.

The picture on the next page shows the average (mean) level of HbA_{1c} before treatment and after 2 and 4 years of treatment for each group. It also shows the change in the HbA_{1c} level from before treatment to the end of 2 and 4 years of treatment for each group.



This picture shows the average HbA_{1c} level at 3 time points: before treatment (light grey bars); the end of the main study after 2 years (medium grey bars); and the end of the extension study after 4 years (black bars). After 2 years, HbA_{1c} changed by -0.66% on average in patients who took empagliflozin and by -0.55% in patients who took glimepiride. After 4 years, HbA_{1c} changed by -0.41% on average in patients who took empagliflozin and by -0.34% 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.

Patients who took empagliflozin had fewer side effects that their doctors thought were related to the study medicine than patients who took glimepiride. About 28.9% of patients taking empagliflozin and 35.5% of patients taking glimepiride had at least 1 such side effect.

Patients who took empagliflozin were less likely to have low blood sugar (hypoglycaemia) (23 patients, or 3.0%) related to study medicine than patients who took glimepiride (155 patients, or 19.9%).

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

	Empagliflozin (765 patients)	**Glimepiride (780 patients)**
Patients with any side effect related to study medicine	221 patients (28.9%)	277 patients (35.5%)
Low blood sugar (Hypoglycaemia)	23 patients (3.0%)	155 patients (19.9%)
High blood sugar (Hyperglycaemia)	21 patients (2.7%)	34 patients (4.4%)
Urinary tract infection	56 patients (7.3%)	54 patients (6.9%)
Frequent urination or peeing (Pollakiuria)	22 patients (2.9%)	6 patients (0.8%)
Large amounts of urine or pee (Polyuria)	15 patients (2.0%)	0 patients (0.0%)
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: 48 patients (6.3%) in the empagliflozin group and 52 patients (6.7%) in the glimepiride group.

In the empagliflozin group, 161 patients (21.0%) had at least 1 serious side effect. In the glimepiride group, 153 patients (19.6%) 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.

Sixteen patients died during the 4 years of study treatment. Eight 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.

The lay summary for the initial analysis of 2-year data may also be found at this website.

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.