This is a summary of a clinical study in type 2 diabetes. It is written for the general reader and uses language that is easy to understand. It includes information about how researchers did the study and what the results were. The simplified title for the study is: 'Efficacy and safety of empagliflozin combined with linagliptin in Japanese patients with type 2 diabetes'.

We thank all patients who took part in this study. Through your participation, you helped researchers answer important questions about empagliflozin combined with linagliptin for the treatment of type 2 diabetes.

What was this study about?

This study tested an empagliflozin/linagliptin combination to treat Japanese patients with type 2 diabetes. Researchers wanted to know how well the combination worked compared with linagliptin alone when taken for 24 weeks by these patients. The combination was given as a single tablet. During the study, researchers also collected information on side effects of the study medicines during 52 weeks of treatment.

This study started in May 2015 and finished in March 2017. The sponsor of this study was Boehringer Ingelheim.

Why was the study needed?

Patients may be able to control their blood sugar levels by following a diet and exercise plan. Sometimes, medicine may be needed as well. There is a need to develop medicines that allow patients to control their blood sugar levels over long periods of time with fewer side effects. Linagliptin is often used to control blood sugar levels. When linagliptin alone does not control the blood sugar levels, additional medicines may be needed. In this study, researchers tested a tablet containing linagliptin and empagliflozin. Combining multiple medicines in 1 tablet reduces the number of tablets that patients have to take.

Which medicines were studied?

In this study, the researchers tested a combination of 2 medicines that are used to treat type 2 diabetes:

Empagliflozin: Empagliflozin helps the kidney to remove sugar from the blood. The sugar is removed in the urine. Empagliflozin belongs to a class of medicines called SGLT-2 inhibitors.

Linagliptin: Linagliptin helps the body to produce more insulin. More insulin lowers the amount of sugar in the blood. Linagliptin belongs to a class of medicines called DPP-4 inhibitors.

Who participated in the study?

Patients in this study had type 2 diabetes. They had followed a diet and exercise plan, but still had high blood sugar. Some patients had not been treated for their diabetes, and others had taken 1 oral antidiabetic medicine.

A total of 275 patients took part in the comparison of the combination treatment with the linagliptin treatment: 214 men (78%) and 61 women (22%). The average age was 60 years. The youngest patient was 32 years old and the oldest patient was 82 years old. The study was done in Japan.

How was this study done?

At the beginning of the study, patients took 5 milligrams (mg) of linagliptin daily for 16 weeks. After this, the patients who still had high blood sugar continued the study. They participated in the Main Phase of the study, followed by the Extension Phase.

Main Phase (24 weeks)

The patients were divided into 2 treatment groups:

- Two thirds of the patients took a tablet containing 10 mg of empagliflozin and 5 mg of linagliptin.
- The remaining one third of the patients took only 5 mg of linagliptin.

It was decided by chance which patient got into which group. Neither the patients nor the study doctors knew which study medicines the patients took. The patients took their medicines each day for 24 weeks.

Extension Phase (28 weeks)

After the Main Phase, patients continued in the same treatment groups for an additional 28 weeks. If patients still had high blood sugar after treatment with the combination in the Main Phase, they received a higher dose in the Extension Phase (a tablet containing 25 mg of empagliflozin and 5 mg of linagliptin). The Extension Phase allowed researchers to learn about the long-term effects of the medicines.

The researchers wanted to know how the medicines affected the amount of sugar in the blood. To do this, they measured the amount of a protein called glycated haemoglobin (HbA_{1c}) in the blood. Patients whose blood sugar is not well controlled have high HbA_{1c} levels. The researchers compared the patients' HbA_{1c} levels at the beginning of the Main Phase with their levels after 24 weeks of treatment. In addition, they collected information on the side effects of the study medicines.

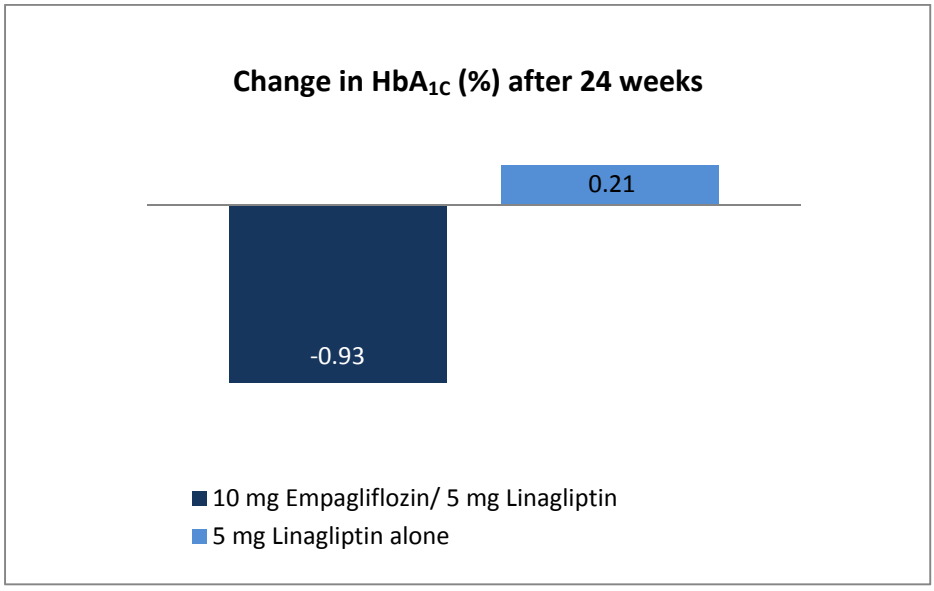
What were the results of this study?

The researchers compared the patients' HbA_{1c} levels at the beginning of the Main Phase with their levels after 24 weeks of treatment.

Was there a greater reduction in HbA_{1c} levels in patients who took the combination?

Yes. After 24 weeks of treatment, there was a greater reduction in HbA_{1c} levels in patients who took the empagliflozin/linagliptin combination than in patients who took linagliptin alone. Researchers used statistical tests on the results. They found that the difference in results between the treatment groups was not likely due to chance.

The picture below shows the average change in the HbA_{1c} level from the beginning of the Main Phase to after 24 weeks of treatment for each group. The HbA_{1c} level decreased by 0.93% in patients who took the empagliflozin/linagliptin combination over 24 weeks. The HbA_{1C} level increased by 0.21% in patients who took linagliptin alone.



What side effects did patients have?

Main Phase

During 24 weeks of treatment, about 15% of patients who took the empagliflozin/linagliptin combination and 3% of patients who took linagliptin alone had at least 1 side effect.

Entire Study (Main Phase plus Extension Phase)

During 52 weeks of treatment, about 20% of patients who took the empagliflozin/linagliptin combination (low dose or high dose) and 8% of patients who took linagliptin alone had at least 1 side effect.

The table below shows side effects that occurred in more than 1 patient in either treatment group through Week 52.

Doctors keep track of all health problems patients have during a study. Some of these health problems might be caused by the study medicines, and some by other medicines taken by the patient. Others might be caused by the disease, and some have yet a different cause. Here we describe health problems that the doctors thought might be caused by the study medicine. These health problems are called side effects.

Side effects during 52 weeks of treatment	**Empagliflozin /Linagliptin Combination (182 patients)**	**Linagliptin Alone (93 patients)**
Patients with any side effect	37 patients (20%)	7 patients (8%)
Increase in a type of molecule produced by the liver (blood ketone body increased)	8 patients (4%)	1 patient (1%)
Bacteria in the urine (asymptomatic bacteriuria)	6 patients (3%)	3 patients (3%)
Bladder infection (cystitis)	4 patients (2%)	1 patient (1%)
Frequent urination (pollakiuria)	4 patients (2%)	0
Thirst	3 patients (2%)	0
Constipation	3 patients (2%)	0
Low blood sugar (hypoglycaemia)	2 patients (1%)	1 patient (1%)
Rash	2 patients (1%)	0
Vaginal itch (vulvovaginal pruritus)	2 patients (1%)	0
Vaginal yeast infection (vulvovaginal mycotic infection)	2 patients (1%)	0

Some patients in the study had serious side effects. A side effect was serious if it caused the patient to go to the hospital or stay longer in the hospital. Or if it needed a doctor's immediate attention, was life-threatening, or caused death.

During 52 weeks of treatment, 3 patients in the empagliflozin/linagliptin combination group and no patient in the linagliptin alone group had serious side effects. These side effects included bleeding in the brain (cerebral haemorrhage), lung cancer (lung neoplasm malignant), and adrenal gland tumor (adrenal neoplasm).

One patient died during the study. This was the patient in the empagliflozin/linagliptin combination group who had bleeding in the brain. The study doctor thought that this death due to bleeding in the brain could be related to the study medicine.

Are there follow-up studies?

No follow-up studies are planned.

Where can I find more information?

You can find the scientific summaries of the study results at these websites:

www.trials.boehringer-ingelheim.com	search for the study number: 1275.19
www.clinicaltrials.gov	search for the NCT number: NCT02453555

The full title of the study is:

'A phase III, randomised, double-blind, parallel group, 52-week study to evaluate efficacy and safety of once daily empagliflozin and linagliptin fixed dose combination compared with linagliptin plus placebo in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control after 16 weeks treatment with once daily linagliptin 5 mg'.

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.