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 empagliflozin 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 24 weeks and 52 weeks of treatment.

This study started in May 2015 and finished in June 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. Empagliflozin is used to control blood sugar levels. When empagliflozin alone does not control the blood sugar levels, additional medicines may be needed. In this study, researchers tested a tablet containing empagliflozin and linagliptin. 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 kidneys 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. The study was carried out in Japan.

A total of 447 patients took part in the comparison of the combination treatment with empagliflozin treatment alone. Patients were divided into 2 groups:

Group A consisted of 215 patients: 170 men (79% of patients) and 45 women (21%). The average age was 57 years. The youngest patient was 30 years old and the oldest patient was 82 years old.

Group B consisted of 232 patients: 166 men (72% of patients) and 66 women (28%). The average age was 58 years. The youngest patient was 28 years old and the oldest patient was 83 years old.

How was this study done?

At the beginning of the study, patients were divided into 2 groups. For 16 weeks, patients in Group A took 10 milligrams (mg) of empagliflozin daily and patients in Group B took 25 mg of empagliflozin daily. After this, the patients who still had high blood sugar continued in the study to test the combination treatment.

In each group, it was decided by chance who got the combination treatment and who got only empagliflozin. Neither the patients nor the study doctors knew which treatment the patients received.

Group A
Half of the patients in this group took a tablet containing 10 mg of empagliflozin and 5 mg of linagliptin. The other half took a tablet containing only 10 mg of empagliflozin. The patients took the medicines each day for 24 weeks.

Group B
Half of the patients in this group took a tablet containing 25 mg of empagliflozin and 5 mg of linagliptin. The other half took a tablet containing only 25 mg of empagliflozin. The patients took the medicines each day for 52 weeks.

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 combination treatment period with their levels after 24 weeks of treatment. In addition, they collected information on the side effects of the study medicines.

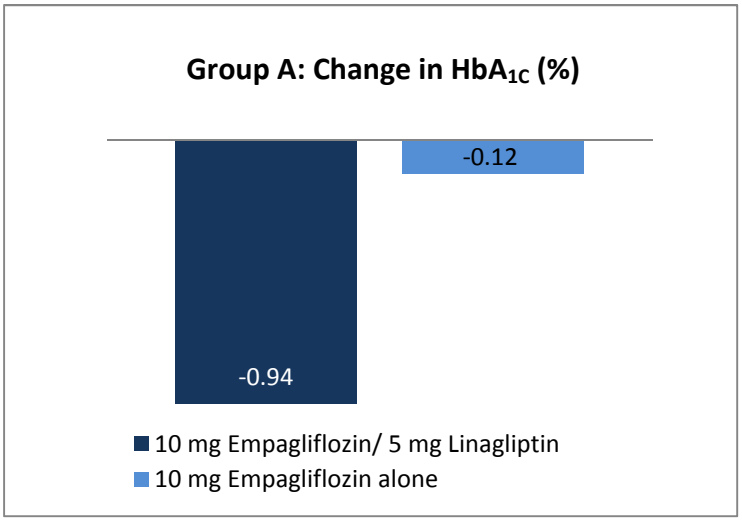
What were the results of this study?

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

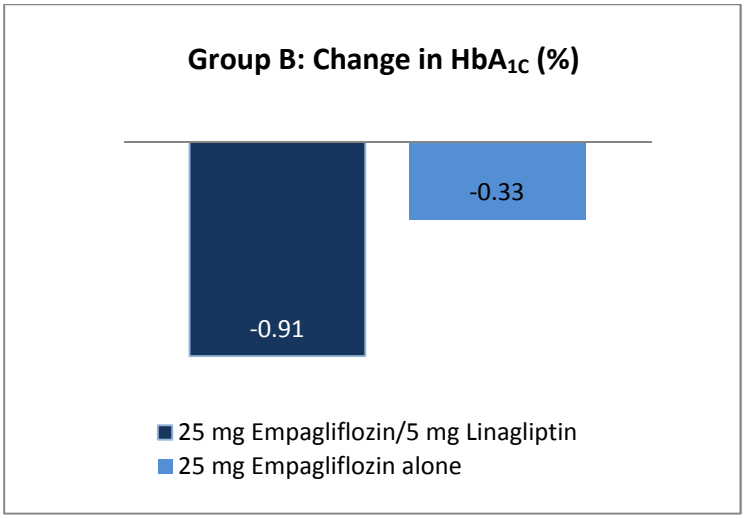
Was there a greater reduction in HbA_{1c} levels in patients who took the combination?

Yes. In both groups of the study, there was a greater reduction in HbA_{1c} levels in patients who took the empagliflozin/linagliptin combination than in patients who took empagliflozin 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 first picture below shows the average change in the HbA_{1c} level from the beginning of the combination treatment period to after 24 weeks of treatment for Group A. The HbA_{1c} level decreased by 0.94% in patients who took the 10 mg empagliflozin/ 5 mg linagliptin combination and by 0.12% in patients who took 10 mg of empagliflozin alone.



The picture below shows the average change in the HbA_{1c} level from the beginning of the combination treatment period to after 24 weeks of treatment for Group B. The HbA_{1c} level decreased by 0.91% in patients who took the 25 mg empagliflozin/ 5 mg linagliptin combination and by 0.33% in patients who took 25 mg of empagliflozin alone.



What side effects did patients have?

In Group A, about 12% of patients who took the empagliflozin/linagliptin combination and 15% of patients who took empagliflozin alone had at least 1 side effect.

The table below for Group A shows side effects that occurred in more than 1 patient in either treatment group during 24 weeks of treatment.

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 problems that the doctors thought might be caused by the study medicine. These health problems are called side effects.

Group A: **Side effects during 24 weeks of treatment**	**10 mg Empagliflozin/ 5 mg Linagliptin Combination (107 patients)**	**10 mg Empagliflozin Alone (108 patients)**
Patients with any side effect	13 patients (12%)	16 patients (15%)
Increase in an enzyme produced by the pancreas (lipase increased)	3 patients (3%)	0
Increase in a type of molecule produced by the liver (blood ketone body increased)	2 patients (2%)	9 patients (8%)

In Group B, about 22% of patients who took the empagliflozin/linagliptin combination and 17% of patients who took empagliflozin alone had at least 1 side effect during 24 weeks of treatment.

On the next page, the first table for Group B shows side effects that occurred in more than 1 patient in either treatment group during 24 weeks of treatment.

Group B: **Side effects during 24 weeks of treatment**	**25 mg Empagliflozin/ 5 mg Linagliptin Combination (116 patients)**	**25 mg Empagliflozin Alone (116 patients)**
Patients with any side effect	25 patients (22%)	20 patients (17%)
Increase in a type of molecule produced by the liver (blood ketone body increased)	11 patients (10%)	5 patients (4%)
Bacteria in the urine (asymptomatic bacteriuria)	3 patients (3%)	3 patients (3%)
Weight decreased	2 patients (2%)	5 patients (4%)
Breakdown of fats that causes increase in ketone bodies (ketosis)	2 patients (2%)	0
Having a type of molecule produced by the liver in the urine (urine ketone body present)	2 patients (2%)	0
Vaginal yeast infection (vulvovaginal mycotic infection)	0	2 patients (2%)

In Group B, about 28% of patients who took the empagliflozin/linagliptin combination and 20% of patients who took empagliflozin alone had at least 1 side effect during 52 weeks of treatment. The table below shows side effects that occurred in more than 1 patient in either treatment group during 52 weeks of treatment.

Group B: **Side effects during 52 weeks of treatment**	**25 mg Empagliflozin/ 5 mg Linagliptin Combination (116 patients)**	**25 mg Empagliflozin Alone (116 patients)**
Patients with any side effect	33 patients (28%)	23 patients (20%)
Increase in a type of molecule produced by the liver (blood ketone body increased)	16 patients (14%)	9 patients (8%)
Bacteria in the urine (asymptomatic bacteriuria)	4 patients (3%)	3 patients (3%)
Having a type of molecule produced by the liver in the urine (urine ketone body present)	4 patients (3%)	0
Increase in broken down fats in blood (free fatty acids increased)	3 patients (3%)	0
Weight decreased	2 patients (2%)	5 patients (4%)
Breakdown of fats that causes increase in ketone bodies (ketosis)	2 patients (2%)	0
Constipation	1 patient (1%)	2 patients (2%)
Vaginal yeast infection (vulvovaginal mycotic infection)	1 patient (1%)	2 patients (2%)

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, or was life-threatening.

In Group A, there were no serious side effects.

In Group B, 1 patient taking the empagliflozin/linagliptin combination had a serious side effect (medicine-induced liver injury).

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: 1275.13
www.clinicaltrials.gov	search for the NCT number: NCT02489968

The full title of the study is:

'A phase III, randomised, double-blind, parallel group, 24-week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and linagliptin 5 mg fixed dose combination compared with empagliflozin 10 mg plus placebo and a 52-week study to evaluate efficacy and safety of once daily empagliflozin 25 mg and linagliptin 5 mg fixed dose combination compared with empagliflozin 25 mg plus placebo (including a 28-week extension period to investigate the long-term safety) in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16-week treatment with empagliflozin (10 mg or 25 mg) alone once daily'.

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.