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GLYXAMBI CLINICAL TRIAL REPRINT

COMBINATION OF EMPAGLIFLOZIN AND LINAGLIPTIN AS SECOND-LINE THERAPY IN SUBJECTS WITH TYPE 2 DIABETES INADEQUATELY CONTROLLED ON METFORMIN

DeFronzo RA, Lewin A, Patel S, et al. *Diabetes Care*. 2015; DOI: 10.2337/dc14-2364

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INDICATIONS AND LIMITATIONS OF USE

GLYXAMBI is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin, a component of GLYXAMBI, is indicated to reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus and established CV disease. However, the effectiveness of GLYXAMBI on reducing the risk of CV death in adults with type 2 diabetes mellitus and CV disease has not been established.

GLYXAMBI is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. GLYXAMBI has not been studied in patients with a history of pancreatitis, and it is unknown if using GLYXAMBI increases the risk of developing pancreatitis in these patients.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: Severe renal impairment, end-stage renal disease, or dialysis; Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity.

Please see additional Important Safety Information on adjacent pages. Please see Prescribing Information, including Medication Guide.

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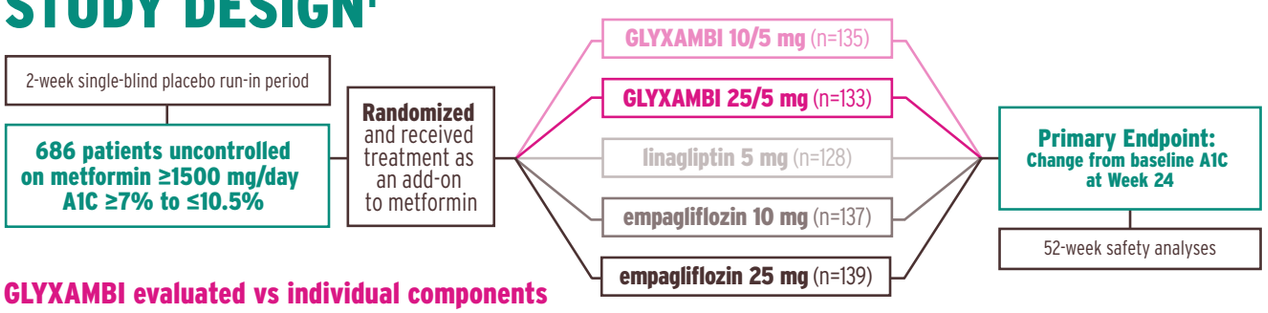
OBJECTIVE[1]

- To evaluate the efficacy and safety of GLYXAMBI vs the individual components of empagliflozin and linagliptin as second-line therapy in adults with type 2 diabetes uncontrolled on metformin

STUDY DESIGN[1]



Primary efficacy endpoint: Change from baseline in A1C at Week 24

One key secondary efficacy endpoint: Change from baseline in body weight at Week 24

STUDY RATIONALE

"...[W]hen metformin fails to achieve glycemic control, add-on combination therapy with 2 oral antidiabetes agents may be beneficial."

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS

Pancreatitis: Acute pancreatitis, including fatal pancreatitis, has been reported in patients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis and, if suspected, promptly discontinue GLYXAMBI and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GLYXAMBI.

Heart Failure: Heart failure has been observed with two other members of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. Consider risks and benefits of GLYXAMBI in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment. Monitor patients for signs and symptoms. Advise patients of the symptoms of heart failure and to immediately report such symptoms. If heart failure develops, consider discontinuation of GLYXAMBI.

Hypotension: Empagliflozin causes intravascular volume contraction and symptomatic hypotension may occur. Before initiating GLYXAMBI, assess and correct volume status in the elderly, and in patients with renal impairment, low systolic blood pressure, or on diuretics. Monitor for hypotension.

Ketoacidosis: Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose cotransporter 2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. Patients who present with signs and symptoms of metabolic acidosis should be assessed for ketoacidosis, even if blood glucose levels are less than 250 mg/dL. If suspected, discontinue GLYXAMBI, evaluate, and treat promptly. Before initiating GLYXAMBI, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis.

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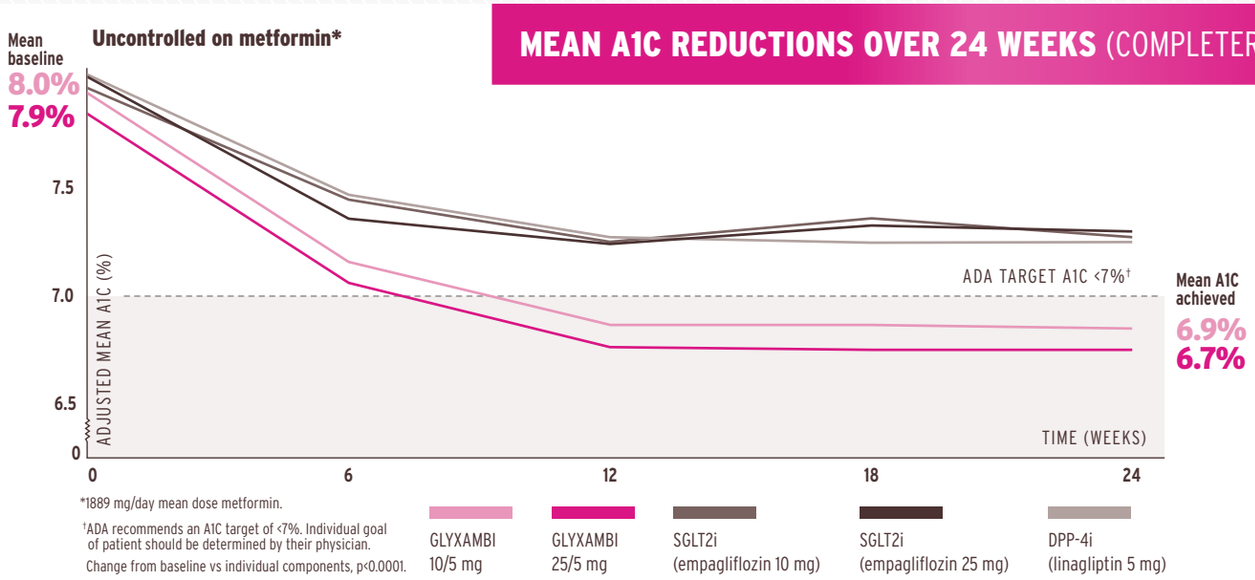
For adults with type 2 diabetes
uncontrolled on metformin
in addition to diet and exercise

SUPERIOR A1C REDUCTIONS
vs each individual component

MEAN A1C REDUCTIONS OVER 24 WEEKS (COMPLETERS)[2]



Individual component mean A1C achieved from the completer analysis: 7.3% for linagliptin 5 mg, 7.3% for empagliflozin 10 mg, 7.3% for empagliflozin 25 mg.[2]

In the modified intent-to-treat analysis of the primary endpoint, the adjusted mean A1C change from baseline for GLYXAMBI 10/5 mg was -1.1% (n=135); GLYXAMBI 25/5 mg, -1.2% (n=133); linagliptin 5 mg, -0.7% (n=128); empagliflozin 10 mg, -0.7% (n=137); empagliflozin 25 mg, -0.6% (n=139). GLYXAMBI vs individual components, p<0.0001.[2]

In patients uncontrolled on metformin with a mean baseline of 9.1% (subgroup analysis)‡

MEAN A1C CHANGE IN PATIENTS WITH BASELINE ≥8.5% AT WEEK 24[1]

-1.6% **GLYXAMBI** 10 mg (n=30, mean baseline: 9.1%)

-1.8% **GLYXAMBI** 25 mg (n=32, mean baseline: 9.1%)

SGLT2i: Empagliflozin 10 mg (n=35, mean baseline 9.3%): **-1.3%**

SGLT2i: Empagliflozin 25 mg (n=36, mean baseline 9.2%): **-1.2%**

DPP-4i: Linagliptin 5 mg (n=33, mean baseline 9.3%): **-1.0%**

‡Exploratory endpoint; ≥8.5% baseline stratified at randomization.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Acute Kidney Injury and Impairment in Renal Function: Empagliflozin causes intravascular volume contraction and can cause renal impairment. Acute kidney injury requiring hospitalization and dialysis have been identified in patients taking SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age. Before initiating GLYXAMBI, consider factors that may predispose patients to acute kidney injury. Consider temporary discontinuation in settings of reduced oral intake or fluid losses. Monitor patients for signs and symptoms of acute kidney injury. If it occurs, discontinue GLYXAMBI and treat promptly.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Before initiating GLYXAMBI, evaluate renal function and monitor thereafter. More frequent monitoring is recommended in patients with eGFR <60 mL/min/1.73 m^2. Discontinue GLYXAMBI in patients with a persistent eGFR <45 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis: Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been identified in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate for signs and symptoms of urinary tract infections and treat promptly.

Hypoglycemia: The use of GLYXAMBI in combination with insulin or insulin secretagogues can increase the risk of hypoglycemia. A lower dose of insulin or the insulin secretagogue may be required.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue GLYXAMBI.

Genital Mycotic Infections: Empagliflozin increases the risk for genital mycotic infections, especially in patients with prior infections. Monitor and treat as appropriate.

Hypersensitivity Reactions: Discontinue GLYXAMBI, treat promptly, and monitor until signs and symptoms resolve. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with GLYXAMBI.

Increased Low-Density Lipoprotein Cholesterol (LDL-C): Monitor and treat as appropriate.

Severe and Disabling Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider linagliptin as a possible cause for severe joint pain and discontinue GLYXAMBI, if appropriate.

Bullous Pemphigoid: There have been reports of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue GLYXAMBI.

MOST COMMON ADVERSE REACTIONS (≥5%): urinary tract infections, nasopharyngitis, upper respiratory tract infections.

DRUG INTERACTIONS

Empagliflozin: Coadministration with diuretics may enhance the potential for volume depletion.

Linagliptin: The efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Alternative treatments should be used.

USE IN SPECIAL POPULATIONS

Pregnancy: GLYXAMBI is not recommended, especially during the second and third trimesters.

Lactation: GLYXAMBI is not recommended while breastfeeding.

Geriatric Use: GLYXAMBI is expected to have diminished efficacy in elderly patients with renal impairment. Renal function should be assessed more frequently in elderly patients. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in patients ≥75 years treated with empagliflozin.

CL-GLX-100035 7.12.19

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References: 1. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care*. 2015;38(3):384-393. **2.** Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. 2013.

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