LX4211 Therapy Reduces Postprandial Glucose Levels in Patients With Type 2 Diabetes Mellitus and Renal Impairment Despite Low Urinary Glucose Excretion

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ABSTRACT

Purpose: We sought to assess the efficacy and safety profile of LX4211, a dual inhibitor of sodium-glucose cotransporter1 (SGLT1) and SGLT2, in patients with type 2 diabetes and renal impairment.

Methods: Thirty-one patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 were randomly assigned to receive 400 mg of LX4211 or placebo for 7 days. The primary end point was the change from baseline to day 7 in postprandial glucose (PPG) levels. Other end points included changes in fasting plasma glucose levels, glucagon-like peptide 1 levels, urinary glucose excretion (UGE), and blood pressure.

Findings: LX4211 therapy significantly reduced PPG levels relative to placebo in the total population and in patients with an eGFR <45 mL/min/1.73 m^2, with a placebo-adjusted decrease in incremental $AUC_{predose–4}$ of 73.5 mg · h/dL ($P = 0.009$) and 137.2 mg · h/dL ($P = 0.001$) for the total population and the eGFR <45 mL/min/1.73 m^2 subgroup, respectively. There was a significant reduction in fasting plasma glucose levels relative to baseline of –27.1 mg/dL ($P < 0.001$). Total and active glucagon-like peptide 1 levels were significantly elevated relative to placebo with LX4211 dosing, and UGE was significantly elevated with placebo-subtracted measures of 38.7, 53.5, and 20.4 g/24 h ($P \leq 0.007$ for all 3) in the total population, eGFR 45 to 59 mL/min/1.73 m^2, and eGFR <45 mL/min/1.73 m^2 subgroups, respectively.

Implications: The PPG effects were maintained in patients with an eGFR <45 mL/min/1.73 m^2 despite the expected reduction in UGE, suggesting that dual SGLT1 and SGLT2 inhibition with LX4211 could prove useful for the treatment of patients with type 2 diabetes and renal impairment. ClinicalTrials.gov identifier: NCT01555008. (*Clin Ther.* 2015;37:71–82)

Key words: fasting plasma glucose, LX4211, pharmacokinetics, postprandial glucose, renal impairment, SGLT1, SGLT2, urinary glucose excretion.

INTRODUCTION

Type 2 diabetes mellitus, a growing public health concern, affects approximately 29 million people in the United States alone, and an additional 86 million patients have prediabetes.[1] Type 2 diabetes is a major risk factor for progressive chronic kidney disease (CKD), and since 1988 there has been a steady increase in the prevalence of patients in the United States with type 2 diabetes and moderate to severe CKD, defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2.[2] By 2006, 17% to 18% of US patients known to have type 2 diabetes, nearly 3 million people, were in this GFR range,[2–4] as were an estimated 10% of US patients with prediabetes, defined as a fasting blood glucose level >100 and <126 mg/dL.[5]

Patients with type 2 diabetes are at increased risk for cardiovascular (CV) disease, the leading cause of morbidity and mortality for these patients.[6] This increased CV risk seems to be largely limited to the subgroup of patients with CKD as patients with type 2 diabetes and without nephropathy have a similar mortality risk compared with patients without

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diabetes.[7–9] Hyperglycemia is one of the modifiable risk factors for CKD, and studies suggest that glycemic control can reduce the risk of microvascular complications and reduce the progression of CKD.[10–15] However, once renal impairment is present, patients with diabetes are at increased risk for hypoglycemia and drug-drug interactions, due to decreased kidney gluconeogenesis and decreased renal clearance of insulin and other drugs, thereby limiting their treatment options.[16,17]

The National Kidney Foundation (NKF) has released guidelines recommending a decreased dosage of some oral antidiabetes (OAD) agents and avoidance of others for patients with CKD.[18] Options become increasingly restricted for patients with diabetes and a GFR <60 mL/min/1.73 m^2. As a result, many of these patients with renal impairment use insulin therapy despite the risk of hypoglycemia. Notwithstanding recommendations, studies indicate that $<50\%$ of patients with type 2 diabetes and CKD are treated in accordance with NKF guidelines, and only 25.6% are treated in accordance with prescribing information.[19–21] Discordance with treatment guidelines results in poorer glycemic control, increased risk of severe hypoglycemic events, and, in some studies, more inpatient hospitalizations and elevated treatment cost. Thus, there is a need for adherence to guidelines for currently available antidiabetes agents and new treatment options.

The selective sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a new class of OAD agents that work by blocking renal glucose reabsorption.[22] By increasing urinary glucose excretion (UGE), these agents improve glycemic control by an insulin-independent mechanism while also decreasing weight and blood pressure (BP) through caloric loss and osmotic diuresis, respectively. However, because of their reliance on kidney function, UGE and the resulting reduction in the glycosylated hemoglobin (HbA_{1c}) level are diminished as GFR is decreased. In contrast, LX4211 is a dual inhibitor of SGLT1 and SGLT2 that is designed to delay glucose absorption in the gastrointestinal tract, triggering elevated postprandial glucagon-like peptide 1 (GLP-1) and peptide YY release via SGLT1 inhibition and blocking renal glucose reabsorption via SGLT2 inhibition.[23–26] Multiple-dose (28-day) administration of LX4211 as monotherapy in patients with diabetes decreased HbA_{1c}, PPG, and fasting plasma glucose (FPG) levels.[23] In an additional 12-week study, dosing LX4211 on top of stable-dose metformin produced reductions in HbA_{1c} concentrations, FPG levels, weight, and BP.[27] As the dose increased in this study, further HbA_{1c} reductions were produced in the absence of additional UGE, suggesting that the SGLT1 inhibition with LX4211 was clinically meaningful. Theoretically, any benefits obtained with LX4211 through inhibition of intestinal SGLT1 should not be diminished in patients with a decreased GFR.

This study was conducted to determine whether the activity of LX4211 is maintained in patients with type 2 diabetes and moderate to severe renal impairment (defined by an estimated GFR [eGFR] <60 mL/min/1.73 m^2) as assessed by the pharmacodynamic (PD) measures of PPG and FPG. In addition, the pharmacokinetic (PK) properties of LX4211 were characterized to determine whether the metabolism of LX4211 is modified in this patient population, and the study provided a first opportunity to assess the tolerability of LX4211 in patients with moderate to severe renal impairment.

PATIENTS AND METHODS

Study Design

This double-blind placebo-controlled study consisted of several study periods: Screening (Days –42 to Day 1), a 5-day Washout (Days –7 to -2) of any ongoing therapy for glucose, and a 7-day Treatment period. During Washout, patients discontinued any combination antidiabetes therapy and continued either a lifestyle or a diet-controlled regimen, basal (long-acting) insulin (ie, insulin glargine or insulin detemir only), or 1 permissible OAD agent (ie, a biguanide, a dipeptidyl peptidase 4 inhibitor, or thiazolidinedione). Patients who did not need medication washout were required to perform the 7-point finger-stick blood glucose (FSBG) test to demonstrate achievement of a daily fasting blood glucose level within the range ≥ 100 and ≤ 270 mg/dL for ≥ 2 consecutive days before day –2 and to be on a stable antidiabetes drug therapy regimen for ≥ 5 consecutive days before day –2. LX4211 (2 x 200 mg) or placebo tablets were administered within 5 minutes before breakfast on day 1. At the investigator's discretion, patients were released to return home on day 3, 4, or 5 with instructions to return for an outpatient visit on day 4. While outpatients, the patients continued