BIOBUSINESS BRIEFS

TRIAL WATCH

SGLT2 inhibitor shows promise in type 2 diabetes

Lexicon Pharmaceuticals has reported that LX4211, an inhibitor of the sodium-dependent glucose transporter 2 (SGLT2; also known as SLC5A2), significantly improved glycaemic control in a Phase II trial of patients with type 2 diabetes.

In the study, subjects were sequestered, provided with a controlled diet and randomized to receive placebo ($n = 12$) or oral LX4211 at a dosage of 150 mg ($n = 12$) or 300 mg ($n = 12$), once daily for 28 days. Average percent glycated haemoglobin A1c (HbA1c), a measure of blood glucose levels over time, was reduced by 1.15% in the 150 mg dosage group and by 1.25% in the 300 mg dosage group, compared with 0.49% in the placebo group. For half the patients in both groups that received LX4211, HbA1c levels were reduced to ≤7% (indicating satisfactory glycaemic control).

Glucose in the circulation is filtered in the glomeruli of the kidneys and then reabsorbed via SGLT2 in the renal proximal tubules. So, inhibition of SGLT2 suppresses renal glucose reabsorption and effectively increases urinary glucose excretion and reduces calorific load. The potential of SGLT2 inhibitors to reduce plasma glucose levels without inducing increased insulin secretion or sensitivity, or causing hypoglycaemia, has encouraged the development of multiple drugs in this class, the most advanced of which have reached Phase III trials (BOX 1).

According to Serge Jabbour, Professor of Medicine in the Division of Endocrinology, Diabetes and Metabolic Diseases at Thomas Jefferson University, USA, an SGLT2 inhibitor could offer several advantages over current diabetes therapies. "As well as their lack of risk of hypoglycaemia, by improving glycaemic control and by virtue of their insulin-sparing effects, SGLT2 inhibitors may help to interrupt the vicious cycle of β-cell destruction, improve insulin action and possibly lead to β-cell preservation." In addition: "SGLT2 inhibitors, unlike thiazolidinediones [a commonly used class of diabetes drugs], have a tendency to increase fluid excretion by a mechanism that depends on osmotic diuresis. This is very important since many diabetics may have underlying heart disease and any fluid overload could precipitate heart failure."

In the study, patients in both dosage groups also had weight reduction accompanied by decreased blood pressure and lower levels of triglycerides. According to Lexicon Pharmaceuticals, the magnitude of and rapid response in glyacemic control, combined with the triglyceride reduction, may distinguish LX4211 from other agents in this class (BOX 1). However, as Jabbour notes: "Although SGLT2 inhibitors also lead to weight loss, we do not know whether the loss of calories in the form of urinary glucose will lead to a compensatory increase in feeding (in a non-controlled environment)."

LX4211 also had a favourable safety profile, with no dose-limiting toxicities. "The most compelling evidence for the safety of SGLT2 inhibitors comes from individuals with a condition known as familial renal glucosuria, who have a defective form of SGLT2 that leads to significant urinary excretion of glucose. These patients have normal kidney function, are not hypoglycaemic and have no electrolyte imbalance or increased frequency of urinary tract infections," concludes Jabbour.

Box 1 | **SGLT2 inhibitors in trials for type 2 diabetes**

Listed below are sodium-dependent glucose transporter 2 (SGLT2) inhibitors that are currently in clinical trials for type 2 diabetes. Data obtained from the Investigational Drugs database from Thomson Reuters.

Phase III

Canagliflozin (Mitsubishi Tanabe Pharma, Johnson & Johnson)*, dapagliflozin‡ (Bristol–Myers Squibb, AstraZeneca).

Phase II

ASP1941 (Kotobuki Pharmaceutical, Astellas Pharma), BI10773 (Boehringer Ingelheim), BI44847 (Boehringer Ingelheim), LX4211 (Lexicon Pharmaceuticals), RG7201 (Roche, Chugai Pharmaceutical).

Phase I

ISIS388626 (Isis Pharmaceuticals)

*Also in trials for obesity. ‡Also in trials for type 1 diabetes.