Diabetes is a highly prevalent disease affecting more than 150 million people worldwide.1 Type 2 diabetes mellitus is characterized by disturbed insulin secretion from pancreatic β cells and/or insufficient action of insulin (insulin resistance) in peripheral organs. The mechanism of action of the antidiabetic agents used for the treatment of type 2 diabetes includes increasing insulin release, increasing insulin sensitivity, controlling hepatic glucose release, or inhibiting intestinal glucose absorption.2 Long-term blood glucose control becomes difficult when the treatment is accompanied by body weight gain during the therapeutic process.3 Among commonly used oral hypoglycemic agents, thiazolidinediones and sulfonylurea contribute to weight gain.1,4

The poor glycemic control leaves diabetics susceptible to developing both microvascular and macrovascular complications that increase morbidity and mortality. There is a significant unmet need for effective therapies and shortage of advanced projects targeting new mechanisms of action that have crossed toxicological studies and early clinical development.5 A recent therapeutic approach for long-term successful control of blood sugar and improving insulin resistance in diabetic patients has been energy control in the reverse direction.3 From this point of view, several researchers have focused on SGLT2 to reduce the blood glucose level by blocking the renal glucose reabsorption system.

**RENAL PHYSIOLOGY OF GLYcosURIA**

The kidney plays a critical role in filtration and reabsorption of glucose. One hundred eighty grams of plasma glucose are filtered by the kidney per day, of which 99% is reabsorbed into plasma in the proximal tubules.6 Glucose starts appearing in urine once its levels exceed the maximum capacity (Tm) of the carrier protein, which usually corresponds to a plasma glucose level of 180 mg/dL.7,8
of 200 mg/dL. In patients with diabetes, hyperglycemia results in hyperfiltration of glucose in the kidney, and the increased luminal glucose exceeds the maximum reabsorption rate, resulting in glucosuria.

MECHANISM OF GLUCOSE TRANSPORT ACROSS MEMBRANES

Cell membrane, composed of lipids, is impermeable to glucose, which is a polar compound. Transport of glucose across the cell membrane requires a carrier protein located in the cell membrane. Glucose enters eukaryotic cells via 2 different types of membrane-associated carrier proteins, the facilitative glucose transporters (GLUTs) and the Na-coupled glucose cotransporters (SGLTs). Facilitated diffusion of glucose through the cellular membrane is an energy-independent cellular process, catalyzed by GLUTs. There are 13 members in the GLUT family, each with different substrate specificity, kinetic properties, and tissue expression profiles. GLUT4 is primarily involved in insulin-mediated glucose uptake in muscle and adipose tissue. Glucose transport through the apical membrane of intestinal and kidney epithelial cells depends on the presence of secondary active Na⁺/glucose symporters, SGLT1 and SGLT2. The energy provided by cotransport of Na⁺ ions down their electrochemical gradient is used to concentrate glucose inside the cell.

SGLT2—CARRIER PROTEIN: THE UNIQUE THERAPEUTIC TARGET

The transport of glucose from the tubule into the tubular epithelial cells is accomplished by SGLTs, which belong to a large family of sodium glucose cotransporter SLC5. Two SGLT isoforms have been identified: SGLT2, which is exclusively expressed in the brush border of epithelial cells in S1 and S2 segments of proximal renal tubules, and SGLT1, which is expressed primarily in the small intestine, S3 segment of the proximal tubule of the kidney, and myocardium. About 90% of filtered glucose is reabsorbed through SGLT2. Plasma glucose concentration modulates expression and activity of SGLT2. SGLT2 mRNA levels were found to be elevated in diabetic animal models and in renal proximal tubular cells of diabetic patients. The therapeutic potential of SGLT2 inhibition was established with the discovery of familial renal glucosuria (FRG), owing to a defect in SGLT2 expression in the kidney. Normal renal function, absence of hypoglycemia, and electrolyte imbalance in FRG validate SGLT2 inhibition as a potential therapeutic target in diabetes. The selective inhibition of SGLT2 does not hamper glucose transport in other major organs of the body such as the brain, liver, and muscle.

SGLT2 inhibitors offer a considerable advantage as potential antidiabetic medications because of their ability to increase urinary glucose excretion and subsequent plasma glucose-lowering effect without inducing excessive insulin secretion. An increase in urinary glucose excretion leads to a negative energy balance, making it a unique therapeutic class that reduces body weight in diabetic patients.

PRECLINICAL STUDIES ON SGLT2 INHIBITORS

Phlorizine

Phlorizine, originally isolated from the bark of apple trees, has been known to inhibit SGLT2 and SGLT1 nonselectively for quite some time. Administration of phlorizine to partially pancreatectomized diabetic rats induces glucosuria and lowers blood glucose. Phlorizine produces an active metabolite, aglycone phloretin, which inhibits the facultative glucose transporter. However, clinical development of phlorizine was stopped because of its SGLT1-blocking action, producing unacceptable intestinal toxicity. SGLT2 inhibitor T-1095A and its carbonate prodrug T-1095 have been shown to significantly reduce blood glucose and HbA1c when administered orally to Goto-Kakizaki rats for 32 weeks. Ohsumi et al reported 84% inhibition of 14C glucose uptake through the brush-border membrane in Wistar rats with O-glucoside, a SGLT2 inhibitor.

Dapagliflozin

The preclinical toxicology and animal studies of dapagliflozin included cytochrome P450 inhibition and induction studies, P450 reaction phenotyping, metabolite identification in hepatocytes, and pharmacokinetics in rats, dogs, and monkeys. It was found to be a substrate for P-glycoprotein (P-gp) but not a significant P-gp inhibitor. Dapagliflozin was not found to be an inhibitor or an inducer of human P450 enzymes. The prominent metabolic pathways identified were glucuronidation, hydroxylation, and O-deethylation. Preclinical studies have established that dapagliflozin has good oral absorption, is not significantly influenced when taken with food, has linear pharmacokinetics.
over the dose range of 2.5 to 500 mg/d, has adequate clearance through the kidney, has no residual metabolites with significant pharmacological activity, and has the potential for single daily dosing in humans.\textsuperscript{15,16}

**Sergliflozin**

Sergliflozin, another novel SGLT2 inhibitor, has been reported to have dose-dependent urinary glucose excretion in normal mice, rats, and dogs. This drug also inhibited an increase in plasma glucose without stimulating insulin secretion in a streptozotocin-induced diabetic rat model.\textsuperscript{17} A previous study has reported a reduction in glycated hemoglobin and fasting plasma glucose, as well as improved glycemic response after glucose loading and increased urinary glucose excretion without marked osmotic diuresis and electrolyte imbalance following sergliflozin administration in Zucker fatty rats.\textsuperscript{17} This molecule reported no gastrointestinal side effects such as diarrhea and soft feces as a consequence of inhibition of intestinal SGLT1.\textsuperscript{18}

**Remogliflozin**

Remogliflozin is another novel SGLT2 inhibitor based on benzylpyrazole glucoside. This drug has demonstrated a reduction in the levels of fasting plasma glucose and glycated hemoglobin-increased urinary glucose excretion in a dose-dependent manner in several rodent models. This drug inhibits an increase in postprandial glucose by increasing the urinary glucose excretion. This drug has also demonstrated antihyperglycemic effects in both streptozotocin-induced diabetic rats in oral glucose tolerance and in db/db mice in the fed condition. Remogliflozin etabonate improved hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and insulin resistance in high-fat diet-fed Goto-Kakizaki rats.\textsuperscript{19} Development of this drug has recently been stopped in phase II.\textsuperscript{8} The reason for discontinuation of further clinical development of remogliflozin, as cited by its developer, includes “result of evaluating circumstances including the development status of SGLT2 inhibitors by competitors.”\textsuperscript{20}

**CLINICAL DEVELOPMENT**

**Dapagliflozin**

Dapagliflozin, a C aryl glucoside, is a competitive, reversible, and highly selective inhibitor of SGLT2, and the selectivity for SGLT2 over SGLT1 is 1200-fold compared with phlorizine.\textsuperscript{21} This prominent molecule is currently in phase III clinical trials.

In a recently published phase III multicentric double-blind, parallel-group, placebo-controlled trial, 546 adults with type 2 diabetes who had inadequate glycemic control on daily metformin ≥1500 mg were randomly assigned to receive 1 of 3 doses of dapagliflozin (2.5, 5, and 10 mg) orally once daily or placebo. At 24 weeks, the mean HbA\textsubscript{1c} reduction was reported to be 0.30% in the placebo group in comparison to 0.67% ($P = .002$) in the dapagliflozin 2.5-mg group, 0.70% ($P < .0001$) in the dapagliflozin 5-mg group, and 0.84% ($P < .0001$) in the dapagliflozin 10-mg group. A similar incidence of hypoglycemia was reported with dapagliflozin (2%-4%) and placebo (3%). At 24 weeks, significant reductions in body weight were noted in all dapagliflozin groups in comparison with the placebo group. Urinary glucose excretion increased in all dapagliflozin groups but not in the placebo group. The ratio of urinary glucose to urinary creatinine changed from 10.8 to 32.2 in the dapagliflozin groups versus a 0.7 decrease in the placebo group (creatinine value remained unchanged).\textsuperscript{22}

In another 24-week parallel-group, double-blind, placebo-controlled phase III trial, the efficacy of dapagliflozin was established in 557 treatment-naive patients with type 2 diabetes. Four hundred eighty-five patients with glycosylated hemoglobin (HbA\textsubscript{1c}) 7.0% to 10% were randomly allocated to 1 of the 7 groups to receive once-daily placebo or dapagliflozin 2.5, 5, or 10 mg in the morning (main cohort) or evening (exploratory cohort). The remaining 72 patients with higher HbA\textsubscript{1c} (10.1%-12%) were randomly assigned to 2 groups of either dapagliflozin 5 mg/d or 10 mg/d in the morning. The primary end point of the study was change in HbA\textsubscript{1c} from baseline. At 24 weeks, the mean HbA\textsubscript{1c} changes from baseline were $-0.23\%$ with placebo and $-0.58\%$, $-0.77\%$ ($P = .0005$ vs placebo), and $-0.89\%$ ($P < .0001$ vs placebo) with dapagliflozin 2.5, 5, and 10 mg, respectively, in the main cohort. Data from exploratory cohorts were also consistent with these results. No major incidence of hypoglycemia was reported in any of the dapagliflozin groups.\textsuperscript{23}

The efficacy of dapagliflozin was earlier established in 2 phase II trials. One hundred fifty-one early-stage and 58 late-stage type 2 diabetes mellitus patients were randomly assigned to receive 10 mg or 20 mg once-daily dapagliflozin for 12 weeks. The reduction in HbA\textsubscript{1c} level, loss of body weight, and increase urinary glucose excretion from baseline were reported in both early- and late-stage diabetic patients. Late-stage patients had greater reduction in body weight.
The difference in the amount of urinary glucose excretion between the early- and late-stage patients was not statistically significant.24

**Sergliflozin**

This molecule, derived from the prodrug sergliflozin etabonate, has 90-fold specificity of SGLT2 over SGLT1 compared to phlorizine.8 It increases urinary glucose excretion and subsequently lowers plasma glucose without inducing either hypoglycemia or excessive insulin secretion. The clinical development of sergliflozin was stopped in a phase II trial, and the indication was changed to obesity.8

A single oral dose (5-500 mg) pharmacokinetic and pharmacodynamic study of sergliflozin was conducted in 22 healthy volunteers and 8 patients with type 2 diabetes mellitus. The prodrug sergliflozin etabonate was rapidly and extensively converted to sergliflozin; the latter displayed linear kinetics, reached maximum plasma concentrations at approximately 30 to 45 minutes postdose (t_{max}), and had a plasma elimination half-life (t_{1/2}) of approximately 0.5 to 1 hour. Dose-related glucosuria was produced under fasting conditions and fluid balance. The magnitude and duration of the glucosuric effect closely paralleled plasma sergliflozin concentrations. The doses of sergliflozin were well tolerated without any clinically significant adverse events. The postprandial glucose concentration showed transient attenuation following sergiflozin administration. The fasting plasma glucose value was not significantly altered.25

A recently reported multiple-dose (500 and 1000 mg 3 times daily) pharmacokinetic and pharmacodynamics study of sergliflozin was conducted in 18 healthy obese human volunteers for 14 days. The mean half-life of the active drug ingredient was reported to be 2 hours without any evidence of drug accumulation. The study reported that sergliflozin induced dose-related glucosuria by producing rapid and sustained suppression of renal glucose reabsorption and a transient increase in urinary electrolytes and fluid loss. It also reported rapid dose-related reduction in body weight (mean changes of −0.09, −1.55, and −1.74 kg from baseline to day 15 with placebo, sergliflozin etabonate 500 mg, and sergliflozin etabonate 1000 mg, respectively). Plasma glucose, insulin, and electrolyte levels were unaltered. Both doses were well tolerated without affecting renal function and any clinically significant adverse events.25

**ADVERSE EFFECTS OF SGLT2 INHIBITORS**

Although long-term safety data are lacking, trials to date have generally found dapagliflozin to be safe and well tolerated. Concerns related to SGLT2 inhibition include the fact that by their very nature, they cause glucose elevation in the urine that can lead to urinary tract and genital infections, electrolyte imbalances, and increased urinary frequency. The most frequently reported adverse events in phase II and III trials include constipation, diarrhea, nausea, urinary frequency, and genitourinary infections involving urinary tract infections (UTIs) and vulvovaginal infections.27 In a recently reported phase III clinical trial, UTIs and genital infections were more frequently noted in the dapagliflozin arms compared to the placebo arm.23

**FUTURE OF SGLT2 INHIBITORS**

The SGLT2 inhibitors block transcellular glucose flux in renal epithelial tissue, which in turn reduces intracellular oxidative stress by preventing activation of protein kinase C and advanced glycation end products. This unique property of SGLT2 inhibitors may be useful in preventing the development of albuminuria, expansion of mesangial area, and progression of diabetic nephropathy.28 The renoprotective action of dapagliflozin is currently being tested in diabetic patients with severe hypertension as an add-on with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and in diabetic patients with renal impairment. The diuretic effect observed with dapagliflozin may be useful to control hypertension, an associated finding in patients with type 2 diabetes mellitus. This class of drug has a unique property of inducing weight loss, which could also be effective in the treatment of obesity and metabolic syndrome. Although the early weight loss is due to mild osmotic diuresis, the progressive long-term reduction in body weight is attributed to a reduction of the fat mass, which is attributed to the loss of energy through glucose excretion in urine. This class of drugs may also be useful in type 1 diabetes as its mechanism is insulin independent.21

Currently, the 2 most advanced molecules in the SGLT2 class, dapagliflozin and canagliflozin, are in phase III trials. These drugs are now being tested as monotherapy, add-on therapy with metformin, add-on therapy with thiazolidinedione, add-on therapy with glimeperide, add-on therapy with insulin, and add-on trial with sitagliptin (DPP IV inhibitors; Table I). The results of these trials would be crucial before widespread clinical application of SGLT2 inhibitors begins.

Financial disclosure: none declared.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Official Title of the Clinical Trial</th>
<th>Phase</th>
<th>Special Comments About the Trial</th>
<th>Clinicaltrial.gov Number</th>
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<tr>
<td>Dapagliflozin</td>
<td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control With Diet and Exercise</td>
<td>III</td>
<td>Dapagliflozin as monotherapy</td>
<td>NCT00528372</td>
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<td>Dapagliflozin</td>
<td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination With Metformin in Asian Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone</td>
<td>III</td>
<td>With metformin as add on in patients poorly controlled on metformin</td>
<td>NCT01095666</td>
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<tr>
<td>Dapagliflozin</td>
<td>A 24-week International, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Phase III Study With a 80-week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin Therapy When Added to the Therapy of Patients With Type 2 Diabetes With Inadequate Glycemic Control on Insulin</td>
<td>III</td>
<td>Dapagliflozin add on with insulin in poorly controlled diabetes</td>
<td>NCT00673231</td>
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<td>Dapagliflozin</td>
<td>A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg in Combination With Metformin as Initial Therapy as Compared With Dapagliflozin 10 mg Monotherapy and Metformin Monotherapy in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control</td>
<td>III</td>
<td>Dapagliflozin and metformin combination versus dapagliflozin as monotherapy and metformin monotherapy</td>
<td>NCT00859898</td>
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<td>Dapagliflozin</td>
<td>24-Week, Int., Rand., Double-Blind, Parallel-Group, Multi-Centre, Plac.-Controlled Phase III Study With a 24-Wk Ext. Per. to Eval. the Efficacy and Safety of Dapagliflozin in Comb. With Glimepiride (a Sulphonylurea) in Subjects With Type 2 Diab. Who Have Inadeq. Glycaemic Control on Glimepiride Therapy Alone</td>
<td>III</td>
<td>Combination with glimeperide in patients inadequately controlled on glimeperide</td>
<td>NCT00680745</td>
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<td>Dapagliflozin</td>
<td>A 52-Week International, Multi-centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase III Study With a 156-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination With Metformin Compared With Sulphonylurea in Combination With Metformin in Adult Patients With Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Therapy Alone</td>
<td>III</td>
<td>Dapagliflozin with metformin versus sulfonylurea combination</td>
<td>NCT00660907</td>
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<td>Dapagliflozin</td>
<td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB)</td>
<td>III</td>
<td>Patients with uncontrolled hypertension on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)</td>
<td>NCT01137474</td>
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<td>Dapagliflozin</td>
<td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination With Thiazolidinedione Therapy in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone</td>
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<td>Combination with thiazolidinedione</td>
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### Table I (continued)

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<tr>
<td>Dapagliflozin</td>
<td>A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study With 24 Week Extension to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg/Day in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on a DPP-4 Inhibitor Sitagliptin/-Metformin</td>
<td>III</td>
<td>Add on to metformin and sitagliptin combination</td>
<td>NCT00984867</td>
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<td>Canagliflozin</td>
<td>A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment</td>
<td>III</td>
<td>Patients with renal impairment</td>
<td>NCT01064414</td>
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<tr>
<td>Canagliflozin</td>
<td>A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy</td>
<td>III</td>
<td>Canagliflozin versus sitagliptin in patients on metformin and sulfonylurea</td>
<td>NCT01137812</td>
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<td>Canagliflozin (JNJ 28431754)</td>
<td>A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ 28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus</td>
<td>III</td>
<td>To assess cardiovascular events</td>
<td>NCT01032629</td>
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<td>Sergliflozin (GW 869682)</td>
<td>A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Weight Loss, Safety, Tolerability and Pharmacokinetics in Obese Subjects Following 12-Week Dosing of GW869682, an SGLT2 Inhibitor</td>
<td>II</td>
<td>SGLT2 inhibitors in obesity</td>
<td>NCT00494767</td>
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<td>TA-7284</td>
<td>A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally-Administered SGLT2 Inhibitor TA-7284</td>
<td>II</td>
<td>Safety tolerability and efficacy</td>
<td>NCT01022112</td>
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<td>YM543</td>
<td>A Randomized, Double Blind, Placebo and Active Controlled, Dose Escalation Study to Evaluate the Safety, Tolerability and Potential Efficacy of a 12-Week Treatment With YM543 in Subjects With Type 2 Diabetes Mellitus</td>
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<td>BI 10773</td>
<td>The objective of the current study is to investigate the efficacy, safety, and tolerability of BI 10773 at 2 different doses compared to placebo during long-term treatment (78 weeks) in combination with basal insulin in patients with type 2 diabetes mellitus with insufficient glycemic control.</td>
<td>II</td>
<td></td>
<td>NCT01011868</td>
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REFERENCES


