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MEETING REPORT

LATEST CONCEPTS IN THE TREATMENT OF TYPE 2 DIABETES

HIGHLIGHTS FROM THE 47TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES, HELD SEPTEMBER 12-16, 2011, LISBON, PORTUGAL

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SUMMARY

The European Association for the Study of Diabetes held its 47th Annual Meeting on September 12-16, 2011, in Lisbon, Portugal. This scientific program presented the results of extensive research on various issues of diabetes and related disorders, which gave a broader insight into the pathophysiology of the metabolic process. It also focused on a broad range of new therapeutic possibilities and advances in the management of diabetes and its complications.

Key words: Sodium/glucose cotransporter – G protein-coupled receptor agonists – Glucokinase activators – Glucagon receptor antagonists – Diabetes

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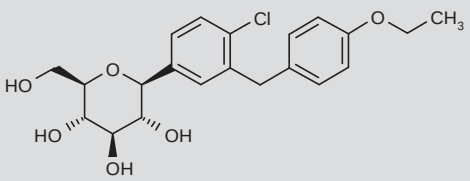
INTRODUCTION

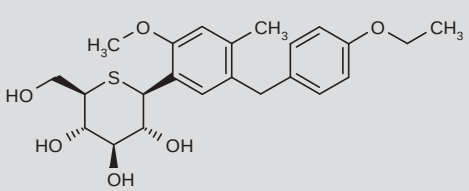
Diabetes is a progressive metabolic disorder characterized by declining beta cell function that, in concert with insulin resistance, leads to loss of glycemic control and eventual diabetic complications. An understanding of pathophysiological abnormalities and treatment of underlying metabolic disturbances can prevent and/or delay the onset of complications. In addition to changes in lifestyle, various antihyperglycemic drugs, either alone or in combination, are commonly employed to aid patients with type 2 diabetes achieve acceptable glycemic targets. A careful selection of different type 2 diabetes therapies is crucial to achieve proper glycemic control while avoiding problems like weight gain and hypoglycemia. Much of the current research in type 2 diabetes is focused on elucidating factors that contribute to the deterioration of beta cell function, with the goal of developing therapeutic options that slow or reverse the course of the disease.

SODIUM/GLUCOSE COTRANSPORTER INHIBITORS

The selective sodium/glucose cotransporter 2 (*SGLT2*) inhibitors reduce hyperglycemia independently of insulin secretion or action by inhibiting renal glucose reabsorption. It has been found that **dapagliflozin** is highly selective for the human transporter and the inhibition constants for dapagliflozin versus sodium/glucose cotransporter 1 (*SGLT1*), sodium/glucose cotransporter KST1, sodium/glucose cotransporter 4 (*SGLT4*) and sodium/glucose cotransporter 6 (*SGLT6*) are 3,000-, 70,000-, 16,500- and 4,050-fold higher, respectively, than sodium/glucose cotransporter 2. This compound has at least 100,000-fold selectivity over solute carrier family 2, facilitated glucose transporter member 1 (GLUT-1), 2 (GLUT-2) and 4



Dapagliflozin

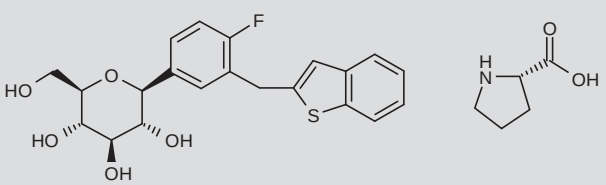


TS-071

(GLUT-4) (1). A randomized, double-blind, placebo-controlled, long-term extension (102 weeks) study added dapagliflozin 2.5, 5 and 10 mg to metformin in patients with type 2 diabetes inadequately controlled with metformin alone. Dapagliflozin demonstrated greater and sustained improvements in glycemic control, a significant reduction in weight and no increased risk of hypoglycemia (2). Another report from 2 randomized, double-blind, active-controlled, 24-week trials revealed that combination of metformin and dapagliflozin was more effective than either drug alone in reducing HbA1c and fasting plasma glucose (FPG), and more effective than metformin in reducing weight when initiated in treatment-naive patients with type 2 diabetes inadequately controlled with diet and exercise (3). In patients with type 2 diabetes who were inadequately controlled on pioglitazone, the addition of dapagliflozin improved HbA1c, FPG and also 120-min postprandial plasma glucose (PPG). Dapagliflozin was well tolerated and mitigated the weight gain of pioglitazone without increasing hypoglycemic risk (4). Dapagliflozin showed sustained glycemic efficacy and weight loss with a low risk of hypoglycemia over 2 years of treatment in patients with type 2 diabetes inadequately controlled with metformin compared with glipizide. Higher frequencies of genital infections and urinary tract infections (UTIs) were reported in the first year, which responded well to the standard treatment (5). Similarly, other pooled data from 12 randomized, placebo-controlled studies suggested that dapagliflozin at doses of ≥ 5 mg/day is accompanied by an increased incidence of UTIs (6). Four placebo- and one active-controlled phase III studies revealed that dapagliflozin is associated with a low frequency of hypoglycemia when used alone or when added to metformin at a fixed dose or titrated in patients with type 2 diabetes (7). These same studies also revealed that dapagliflozin consistently lowered serum uric acid levels, which is an emerging marker for cardiovascular and renal disease risk. Whether this is a direct effect on a uric acid transporter or an indirect effect is unknown and needs further research (8). A 12-week, randomized, double-blind, placebo-controlled, parallel-group study assessed the effects of dapagliflozin 5 mg once daily on insulin sensitivity as measured by glucose disposal rate in subjects with type 2 diabetes and found that there was significant improvement in the overall glucose disposal rate compared with placebo (9). Dapagliflozin was well tolerated by patients with type 2 diabetes and treatment satisfaction was maintained when treatment continued for ≥ 48 weeks (10).

TS-071 is a novel, orally bioavailable, highly selective sodium/glucose transporter 2 inhibitor. TS-071 as a single daily dose reduced HbA1c, FPG and PPG significantly and dose-dependently in patients with type 2 diabetes. It also induced significant body weight reduction without having any major or serious safety concerns (11, 12). Another study indicated that TS-071, either as monotherapy or in combination with metformin, improved glycemic control and also demonstrated significant improvement in the pancreatic beta cell mass in diabetic mice (13).

Ipragliflozin (ASP-1941) is another novel, selective sodium/glucose cotransproter 2 inhibitor. The BRIGHTEN study (double-Blind Randomised study of IpraGliflozin to sHow the efficacy as monotherapy in Type 2 diabetes mellitus patiENts) demonstrated that treatment with ipragliflozin 50 mg once daily reduced HbA1c by 1.23% as compared to placebo after 16 weeks of treatment. In addition, 43.5% of patients in the ipragliflozin group achieved the HbA1c target goal of < 7.4% as compared with 4.5% of patients in the placebo group. Mean body weight was significantly decreased in the ipragliflozin group and there was also a reduction in systolic blood pressure from baseline. The drug was safe and well tolerated (14). Another study investigated the effect of different degrees of renal impairment on the pharmacokinetics and the urinary glucose excretion induced by ipragliflozin in Japanese patients with type 2 diabetes. In patients with moderate renal impairment (eGFR = 30-59 mL/min/1.73m^2), ipragliflozin exposure was increased by 21% and urinary glucose excretion was also reduced (15). Ipragliflozin was found to be safe and well tolerated in patients with type 2 diabetes who were on stable



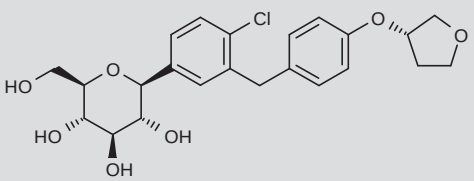
Ipragliflozin

metformin therapy, with no signs of hypoglycemia. Urinary glucose excretion was higher in patients on concomitant treatment of ipragliflozin and metformin compared with patients on metformin and placebo (16).

A double-blind, placebo-controlled 12-week study assessed the efficacy and safety of 5 doses of a potent new sodium/glucose cotransporter 2 inhibitor, **BI-10773,** in patients with type 2 diabetes inadequately controlled on metformin. Significant and dose-dependent reductions in HbA1c versus placebo were shown with BI-10773. Similarly, significant reductions in FPG and body weight versus placebo were observed in all BI-10773 dose groups, except 1 mg, and the drug was well tolerated, with a slightly increased frequency of genital infections but no UTIs (17).

PF-04971729 is a highly potent and selective sodium/glucose cotransporter 2 inhibitor in development for the treatment of type 2 diabetes. In patients with hypertension and type 2 diabetes, administration of once-daily PF-04971729 for 4 weeks resulted in a clinically meaningful decrease in blood pressure and improvement in glycemic control (18). The same group of investigators used PF-04971729 in patients with type 2 diabetes who were inadequately controlled on metformin and found that there was a significant improvement in glycemic control, body weight and blood pressure with PF-04971729, and it was also safe and well tolerated (19).

LX-4211 is a dual inhibitor of sodium/glucose cotransporters 1 and 2, designed to block glucose absorption in the gastrointestinal tract via inhibition of sodium/glucose cotransporter 1 and renal glucose reabsorption via inhibition of sodium/glucose cotransporter 2. LX-4211 improved glycemic control in patients with type 2 diabetes, including FPG, mean plasma glucose and insulin, and also produced significant increases in total and active GLP-1, peptide YY (PYY) and urinary glucose excretion (20).



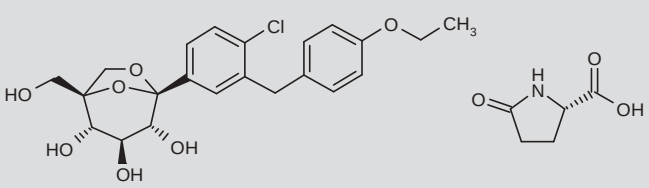
BI-10773

G PROTEIN-COUPLED RECEPTOR AGONISTS

Free fatty acid receptor FFA1 (GPR40) is a G protein-coupled receptor (GPR) highly expressed in pancreatic beta cells that mediates free fatty acid-induced insulin secretion. **TAK-875** is a selective GPR40 agonist that lowers plasma glucose via stimulation of glucose-dependent insulin secretion. The results from a randomized, double-blind, placebo- and active-controlled, dose-ranging study provided evidence of good safety, tolerability and HbA1c-lowering activity for TAK-875 and were consistent with its glucose-dependent mechanism of action (21). Metformin has a pleiotropic action and thus ameliorates insulin resistance. Because of the complementary mechanisms of action, the combination of metformin and TAK-875 is expected to provide an additive improvement in glycemic control. In an animal study the results suggested that combination treatment with metformin and TAK-875 improved glycemic control and has the potential to slow the progression of diabetes and beta cell dysfunction in Zucker diabetic fatty rats, which may result from improvements in both postprandial and fasting hyperglycemia (22).

PSN-821 is a potent, selective, orally administered agonist of the *GPR119* receptor expressed predominantly in pancreatic beta cells and enteroendocrine cells of the gastrointestinal tract in humans. In preclinical animal disease models PSN-821 has been shown to substantially lower blood glucose and also reduce body weight, potentially via modulation of gut hormones, such as GLP-1, gastric inhibitory polypeptide (GIP) and PYY. PSN-821, either alone or in combination with metformin, was found to be effective in lowering both fasting and postprandial glucose. It also suppressed energy intake at higher doses, indicating its weight-lowering potential, and corresponding changes in PYY indicate a possible mechanism for this (23).

GPR119 receptor agonists have the potential to work additively with dipeptidyl peptidase 4 (DPP IV) inhibitors, leading to increased active GLP-1 levels, better glucose control and potential for weight loss in type 2 diabetic patients compared to treatment with a DPP IV inhibitor alone. Using traditional medicinal chemistry techniques, **AR-7947** was identified as a selective small-molecule *GPR119* receptor agonist with good physicochemical characteristics and drug-like



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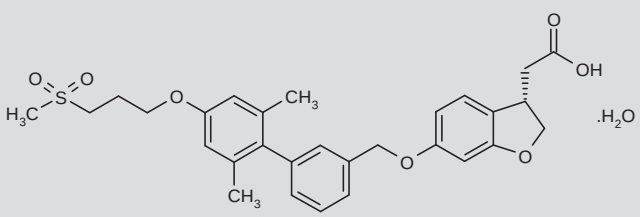


TAK-875

properties. Studies demonstrated that AR-7947 has the potential for durable normalization of glucose and lipid profiles in patients with type 2 diabetes (24).

GLUCOKINASE ACTIVATORS

Glucokinase activators (GKAs) lower the plasma glucose threshold for insulin release and may modulate other hormonal and hepatic mechanisms of glucose homeostasis. **LY-2599506** is an orally administered GKA, found to be well tolerated and to improve FPG and postprandial glucose in patients with type 2 diabetes (25).

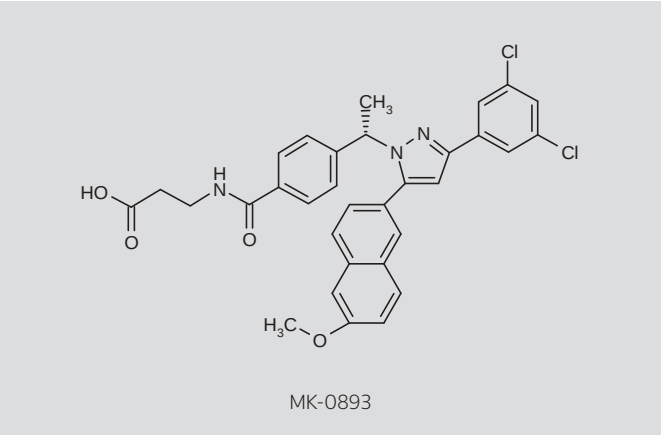
A multiple-ascending-dose study compared the safety, tolerability, pharmacokinetic properties and glucose-lowering potential of **AZD-1656,** a novel GKA, to placebo in patients with type 2 diabetes. AZD-1656 was well tolerated for up to 28 days, the pharmacokinetic parameters were virtually dose- and time-independent, and pharmacodynamic effects were dose-dependent (26). Similarly in Western and Japanese healthy male subjects, AZD-1656 was well tolerated at single doses up to 180 mg and there was no difference in the population pharmacokinetic parameters between these two groups of subjects. A dose-dependent blood glucose-lowering effect of similar magnitude and increased levels of insulin were observed across the populations (27).

Because glucokinase is also present in hypothalamic neurons, it has been hypothesized that glucokinase activation could impair the hypothalamic hormones, which are responsible for the counterregulatory response to hypoglycemia. Studies were done to assess the counterregulatory responses during a stepwise hypoglycemic glucose clamp in healthy male volunteers following a single oral dose of AZD-1656 or **AZD-6370,** another GKA, in comparison to the counterregulatory response to hypoglycemia during an insulin infusion. There was no difference in the counterregulatory response for epinephrine, norepinephrine, growth hormone and cortisol to hypoglycemia induced by either of the GKAs compared to insulin alone. The glucagon counterregulatory response to hypoglycemia was blunted with both GKA compounds compared to insulin, which is likely due to intra-islet hyperinsulinemia induced by GKAs or by local glucokinase activation of the glucokinase receptors known to be present in the alpha cells (28).

GLUCAGON RECEPTOR ANTAGONISTS

Reduction in hepatic glucose production is a key therapeutic goal in patients with type 2 diabetes. Metformin improves glycemic control, in part, by reducing hepatic glucose production. DPP IV inhibitors are responsible for glucose-dependent glucagon suppression and glucose-dependent insulin secretion, and thus reduce hepatic glucose production. Inhibition of glucagon action through blockade of the glucagon receptor may provide a complementary mechanism for further reduction in hepatic glucose production and improvement in glycemic control. **MK-0893** is an oral, highly selective glucagon receptor antagonist in development for the treatment of type 2 diabetes. Initial combination therapy of MK-0893 with metformin or sitagliptin was well tolerated and provided substantial improvements in glycemic control after 4 weeks of treatment (29).

In type 2 diabetes, glucagon levels are inappropriately elevated, promoting hepatic glucose output and contributing to hyperglycemia.



MK-0893

LY-2409021 is a potent, selective glucagon receptor antagonist that attenuates glucagon-induced hepatic glucose output and blood glucose in healthy male subjects (30). LY-2409021 was used as a once-daily treatment for type 2 diabetes and was found to effective in reducing FPG and HbA1c (31, 32).

OTHER NOVEL AGENTS

Inflammation is associated with beta cell apoptosis and reduced insulin sensitivity. IL-1β-mediated inflammation has been implicated in suppression of insulin secretion and worsening of beta cell function, which could be a primary contributor to type 2 diabetes. **Canakinumab** is a human monoclonal anti-human IL-1β antibody of the IgG_{κ} isotype that binds to human IL-1β and thus blocks the interaction of this cytokine with its receptors, thereby neutralizing the activity of IL-1β. Canakinumab, given subcutaneously once a month, lowered HbA1c modestly in metformin-treated type 2 diabetes (33). It also improved the insulin secretion rate in insulin-treated patients with type 2 diabetes, whether using metformin or not, as well as subjects with impaired glucose tolerance (34). These results support the hypothesis that blocking IL-1β in pancreatic islets has the potential to improve beta cell function by reducing suppression of insulin secretion by IL-1β-mediated inflammation.

LY-2189102, a humanized neutralizing IL-1β antibody, was given subcutaneously weekly in patients with type 2 diabetes and was found to be effective in reducing blood glucose and HbA1c. It demonstrated a significant antiinflammatory effect and was well tolerated (35). Pharmacokinetic and pharmacodynamic modeling of subcutaneous LY-2189102 revealed that dosing can be as infrequent as once every 6 weeks without compromising its therapeutic effect, which can be a convenient alternative for patients with type 2 diabetes (36).

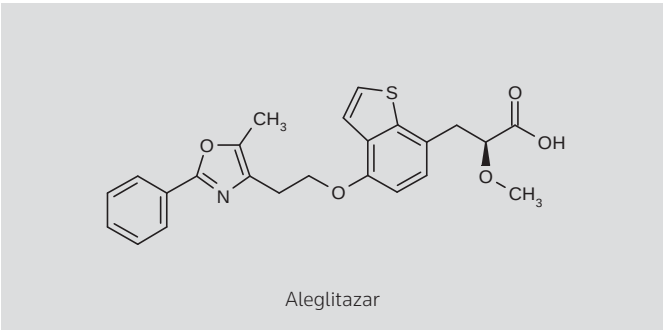
The role of inflammation in diabetes appears to be important, particularly the impact that infiltrating monocytes can have on multiple tissues involved in the disease. Increased adiposity leads to the recruitment of inflammatory myeloid cells into adipose tissue and the production of factors such as TNF-α, IL-6, C-C motif chemokine

2 (monocyte chemoattractant protein 1, MCP-1) and chemokine CCR2 receptor, which are known to impair systemic insulin sensitivity. Myeloid cell recruitment into diabetic liver has been associated with alterations in key metabolic pathways. CCX-140-B is an oral, specific CCR2 receptor antagonist that significantly improved HbA1c in patients with type 2 diabetes and a higher percentage of HbA1c responders was observed after only 4 weeks of treatment. CCX-140-B was well tolerated and safe, and there were no detrimental effects on plasma MCP-1 or blood monocyte levels (37). **CCX-417,** another CCR2 receptor antagonist and an analogue of CCX-140-B, was used in diabetic mice and resulted in robust and rapid improvements of hyperglycemia and glucosuria (38).

Most patients with type 2 diabetes receive treatment for dyslipidemia to help reduce cardiovascular complications. Despite the effects of statin and other therapies, there remains a substantial residual risk of cardiovascular events in the future. **Aleglitazar** is a dual peroxisome proliferator-activated receptor PPARα/γ agonist that significantly improves glycemic control and lipid parameters in patients with type 2 diabetes. In the phase III SYNCHRONY study, aleglitazar 150 μg/day increased apolipoprotein A-I and decreased the levels of apolipoprotein B-100 and fibrinogen. The post hoc subanalysis of SYNCHRONY revealed that aleglitazar treatment reduced LDL cholesterol and triglycerides and increased HDL cholesterol in both statin-treated and statin-free groups of patients with type 2 diabetes (39).

Peripheral insulin resistance, and later insulin deficiency, are key underlying defects in type 2 diabetes. Thiazolidinediones improve insulin sensitivity and diabetes control but are associated with adverse effects, including weight gain and edema. **LIM-0705** is a novel insulin sensitizer under development for the treatment of metabolic diseases. In a study, LIM-0705 inhibited glucose production in hepatocytes through a pathway distinct from thiazolidinediones and metformin, improved glucose infusion rate and insulin-stimulated glucose disposal rate under clamp conditions in the diet-induced obese mouse, and improved 2-hour oral glucose tolerance test in human volunteers. Chronic dosing of LIM-0705 did not cause significant weight changes compared to vehicle (40).

Hepatic glucose output is the major source of glucose in the fasting state. Cortisol is one of the key hormones that promote hepatic glucose output. **KB-003305** is a novel liver-selective glucocorticoid receptor (GR) antagonist and has shown high affinity for the GR in vitro and potent antidiabetic activity in animal models of diabetes. A randomized, double-blind, placebo-controlled, multiple-dose trial demonstrated significantly lower FPG levels with KB-003305 treatment as compared to placebo, without apparent side effects in patients with type 2 diabetes (41).



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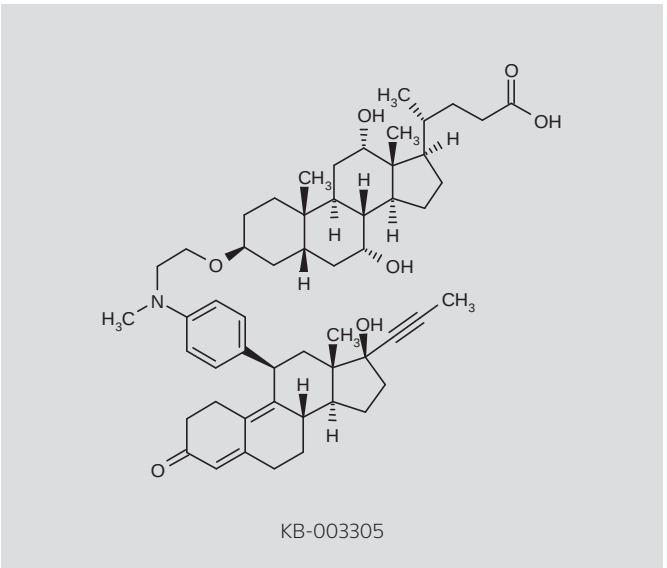

KB-003305

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DISCLOSURES

The author states no conflicts of interest.

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