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R&D INSIGHT REPORT

Luseogliflozin: First Global Approval

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Abstract Luseogliflozin [Lusefi® (Japan)] is an orally active second-generation sodium-glucose co-transporter 2 (SGLT2) inhibitor developed by Taisho Pharmaceutical for the treatment of patients with type 2 diabetes mellitus (T2DM). The drug has received its first global approval for this indication in Japan, either as monotherapy or in combination with other antihyperglycaemic agents. This article summarises the milestones in the development of luseogliflozin leading to this first approval for the treatment of T2DM.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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1 Introduction

Inhibition of renal glucose reabsorption is emerging as a novel therapy for patients with type 2 diabetes mellitus (T2DM). In particular, blocking the sodium-glucose co-transporter 2 (SGLT2)—a low-affinity high-capacity transporter localised to the renal proximal tubules—has been shown to suppress glucose reabsorption, leading to increased urinary excretion with a concomitant reduction in plasma glucose levels. Compounds selective for SGLT2 are desirable as SGLT1 is highly expressed in the gastrointestinal tract but only moderately expressed in the kidneys [1, 2].

Luseogliflozin [Lusefi® (Japan)] is a selective SGLT2 inhibitor, which received its first marketing approval for the treatment of T2DM on the 24th of March 2014. The drug has received approval as 2.5 and 5 mg oral tablets with a recommended starting dose of 2.5 mg once daily. This may be increased to 5 mg once daily if necessary for optimal clinical effect [3, 4].

The approval of luseogliflozin was based on a series of phase III trials in patients with T2DM; all were conducted in Japan in patients of Japanese ethnicity. Two trials evaluated the efficacy of luseogliflozin in combination with other antihyperglycaemic agents in patients with suboptimal glycaemic control on that agent alone, and two trials evaluated luseogliflozin as monotherapy.

1.1 Company Agreements

In November 2012, Novartis licensed the marketing rights for luseogliflozin in Japan. Under the terms of this agreement, luseogliflozin will be manufactured by Taisho Pharmaceutical and co-marketed by both Taisho and Novartis in Japan. Taisho will receive an upfront payment and milestone payments from Novartis [5].

Features and properties of luseogliflozin

Alternative names	Lusefi®; Luseogliflozin hydrate; TS 071; TS-071; TS-71
Class	Phenyl-ethers, Small-molecules, Sugar-alcohols, Sulfides
Mechanism of Action	Sodium-glucose co-transporter 2 inhibitors
Route of Administration	Oral
Pharmacodynamics	Luseogliflozin dose-dependently increases urinary glucose excretion and reduces blood glucose levels. The drug has a 1650-fold greater selectivity for SGLT2 over SGLT1
Pharmacokinetics	Luseogliflozin demonstrates dose proportional pharmacokinetics with no cumulative effect. Mean time to maximum plasma concentration ranged from 0.67 to 2.25 h and mean plasma half-life ranged from 9.2 to 13.8 h
Adverse events	Urinary frequency (2.8 %), hypoglycaemia (2.4 %), increased urinary macroglobulin β2 levels (2.1 %) [4]
ATC codes	
WHO ATC code	A10B (Blood Glucose Lowering Drugs, Excl. Insulins), A10B-X (Other oral blood glucose lowering drugs, excl. insulins)
EphMRA ATC code	A10 (Drugs Used in Diabetes), A10X (Other Drugs Used in Diabetes)
Chemical Name	(2S,3R,4R,5S,6R)-2-[5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl]-6-(hydroxymethyl)tetrahydro-2Hthiopyran-3,4,5-triol

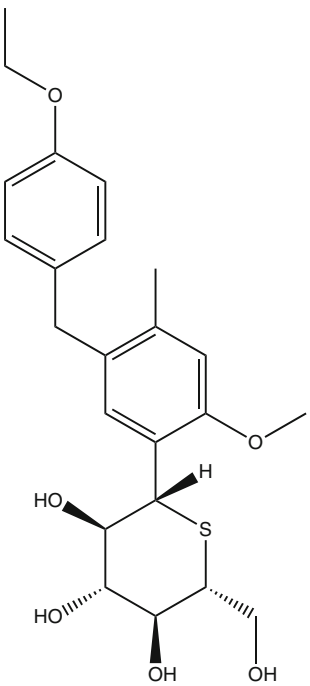
SGLT Sodium-glucose co-transporter

2 Scientific Summary

2.1 Pharmacodynamics

Luseogliflozin is a potent inhibitor of SGLT2 (IC_{50} 2.26 nM) with a 1,650-fold greater selectivity for SGLT2 over SGLT1 [6]. The drug competitively inhibited sodium-dependent ^{14}C-α-methylglucoside uptake (K_i value 1.10 nM) in Chinese hamster ovary-K1 cells overexpressing human SGLT2 in vitro [7]. It also had an apparent 50,000-fold greater selectivity for SGLT2 over glucose transporters based on the results of an in vitro study in 3T3-L1 adipocytes [8]. Oral administration of luseogliflozin at a dose of ≥0.3 mg/kg increased urinary glucose excretion and suppressed postprandial hyperglycaemia in Zucker fatty rats, and reduced non-fasting high glucose levels in *db*/*db* mice. Oral administration of luseogliflozin 0.03 mg/kg to Beagle dogs orally loaded with glucose substantially (107–2,635 fold) increased urinary glucose excretion [8]. In high fat-fed streptozotocin-treated mice, luseogliflozin 10 mg/kg for 12 weeks was associated with a significantly smaller change in plasma haemoglobin A1c (HbA1c) levels (−1.09 vs. 0.33 %; $p < 0.05$) and increased pancreatic insulin contents (53.5 vs. 29.3 μg/g) relative to vehicle. In *db*/*db* mice, luseogliflozin 3 mg/kg significantly decreased fasting plasma glucose (535 vs. 796 mg/dL; $p < 0.001$) and HbA1c levels (6.9 vs. 9.5%; $p < 0.001$) compared with vehicle. Luseogliflozin also restored pancreas β-cell mass and reduced the pancreas α-cell mass compared with vehicle [7].

In Sprague-Dawley rats with diet-induced obesity, oral luseogliflozin 3 or 10 mg/kg once a day for 4 weeks significantly decreased urinary glucose excretion (2,548, 4,938 and 3.1 mg/day; $p < 0.001$), and body weight gain (5.9, 2.2, and 10.5 % change from baseline; $p < 0.05$) compared with vehicle [9].



Chemical structure of luseogliflozin

Luseogliflozin significantly increased urinary glucose excretion in a phase 1 study in male Japanese volunteers. Fifty seven volunteers were randomised to a single dose of luseogliflozin between 1 mg and 25 mg or placebo, and 24 were given the drug at a dosage of 5 or 10 mg/day, or placebo, for seven days. Mean cumulative urinary glucose excretion for 24 h after administration was 18.9, 36.8, 50.2, 54.3, 60.7 and 70.9 g after luseogliflozin 1, 3, 5, 9, 15 and 25 mg, respectively, compared with 0.182 g for placebo. In the multiple dose study, mean daily urinary glucose excretion ranged between 57.2 and 65.5 g with the 5 mg dose and 62.7 and 76.9 g with the 10 mg dose [10]. Luseogliflozin (0.5, 1, 2.5 and 5 mg/day) also produced significant, dose-dependent increases in 24-hour cumulative urinary glucose excretion after 7 days compared with placebo (least squares means of difference from placebo 49.2, 66.5, 89.4 and 101 g/24 h), in a single-blind trial in 40 Japanese patients with T2DM. Endpoint plasma glucose levels after breakfast and lunch were significantly lower with luseogliflozin at all dosages compared with placebo [11].

In a double-blind randomised phase II trial conducted in the United States, seven days' treatment with luseogliflozin at a dose of 1, 2.5, 5, 10, 15 or 25 mg/day stimulated urinary glucose excretion in 72 patients with T2DM. The effect was strongly dose-dependent to 2.5 mg/day with maximum excretion as predicted by modelling (101 g/day) corresponding to the 10 mg/day dose (109 g/day). Plasma glucose exposure was reduced by 25 % ($p = 0.0004$), and mean plasma glucose levels by 60 mg/dL ($p = 0.0003$) at endpoint in patients given luseogliflozin 10 mg compared to placebo. The 10 mg/day optimal dose in this study is higher than the optimal dose in Japanese studies, suggesting that US subjects may require a higher dose [12].

The pharmacodynamic effects of luseogliflozin have also been investigated in patients with T2DM and varying degrees of renal dysfunction. 57 Japanese patients with T2DM and normal (estimated glomerular filtration rate 90 ml/min/1.73m^2) or mildly (60–89 ml/min/1.73 m^2), mild-to-moderately (45–59 ml/min/1.73 m^2), moderate-to-severely (30–44 ml/min/1.73 m^2) or severely (15–29 ml/min/1.73 m^2) impaired renal function were given a single oral 5 mg dose of luseogliflozin. Mean 24-h urinary glucose excretion was significantly increased from baseline levels in all groups (88.3, 69.7, 57.3, 35.3 and 21.8 g, respectively). Postprandial (2 h after breakfast) plasma glucose levels and fasting plasma glucose levels 24 h after administration of luseogliflozin were both reduced significantly from baseline in all but the severe renal impairment group [4, 13].

2.2 Pharmacokinetics

In phase I trials, luseogliflozin exhibited dose-dependent or dose-proportional pharmacokinetics with no cumulative effects. In a single ascending dose study Japanese volunteers received a single dose of luseogliflozin up to 25 mg ($n = 43$) or placebo ($n = 14$). The drug was absorbed quickly with a mean t_{max} of 0.667–2.25 h and exposure (C_{max} and $AUC_{0-\infty}$) increased in a dose-dependent manner. Twenty four volunteers participating in a multiple ascending dose study were given luseogliflozin 5 or 10 mg/day or placebo for seven days. Plasma luseogliflozin concentration-time profiles were similar on days one and seven with both doses. Trough concentrations of the drug had reached steady state by day seven and no accumulation potential was evident [10].

Plasma luseogliflozin concentrations increased dose-dependently in a trial in 40 Japanese patients with T2DM. Luseogliflozin was administered at a dose of 0.5, 1, 2.5 or 5 mg/day for seven days. Plasma luseogliflozin concentrations increased dose-dependently and C_{max} and AUC_{0-T} were dose-proportional on day seven. It was assumed there would be no cumulative effects. Plasma pharmacokinetics in patients in the 5 mg group was similar to those seen in studies in volunteers [11].

In a US study in patients with T2DM, luseogliflozin exhibited dose-dependent pharmacokinetics at dosages of up to 25 mg/day and reached steady state after three days. C_{max} and $AUC_{0-\infty}$ values, however, were lower in this study than the values seen in Japanese studies, suggesting that higher dosages may be required to achieve an equivalent therapeutic effect in US patients [12].

Systemic exposure to luseogliflozin after a single 5 mg dose, as measured by C_{max} and $AUC_{0-\infty}$ levels, was similar in elderly female and male (65–88 years) and younger (21–38 years) male Japanese volunteers indicating dosage adjustment should not be required for age or gender [14].

2.2.1 *Effects of Renal Impairment*

The $AUC_{0-\infty}$ after administration of a single 5 mg oral dose of luseogliflozin was similar in patients with T2DM and normal or mild, moderate or severe, renal function [13].

2.2.2 *Effects on the Pharmacokinetics of other Antihyperglycaemic Agents*

Coadministration of luseogliflozin did not substantially affect the pharmacokinetics of oral glimepiride, metformin, pioglitazone, voglibose or sitagliptin in volunteers indicating that dosage adjustments should not be required should combination therapy with luseogliflozin and any of these agents be considered [15].

2.3 Therapeutic Trials

Luseogliflozin reduced HbA1c and fasting plasma glucose levels both as monotherapy and in combination with other

oral antihyperglycaemic drugs in long-term (24–52 weeks) studies in patients with T2DM. Importantly, treatment with luseogliflozin was also associated with significant reductions in body weight.

2.3.1 Combination Therapy Trials

In a randomised, double-blind phase III trial (JapicCTI111507), the addition of luseogliflozin 2.5 mg once-daily significantly improved diabetic control in Japanese patients with T2DM not adequately controlled by glimepiride monotherapy. HbA1c levels were significantly decreased in the luseogliflozin group versus placebo at week 24 (−0.88 %; $p < 0.001$), and also compared with baseline after 52 weeks (−0.63 %; $p < 0.001$). Fasting plasma glucose and bodyweight were also significantly decreased in the luseogliflozin group at week 24 compared with placebo, and were significantly decreased from baseline at week 52 [16]. In an open-label, placebo-controlled phase III trial (JapicCTI111508) in 487 Japanese patients with T2DM not adequately controlled on existing monotherapy with metformin ($n = 117$), a dipeptidyl peptidase-4 inhibitor ($n = 111$), pioglitazone ($n = 95$), a glinide ($n = 59$), or an α-glucosidase inhibitor ($n = 105$), the addition of luseogliflozin 2.5 or 5 mg once-daily significantly reduced HbA1c. At 52 weeks, the reduction in HbA1c from baseline was −0.52 % to −0.68 % ($p < 0.001$ for all combination regimens). Luseogliflozin also significantly improved fasting blood glucose levels, and significantly lowered body weight in this study [17].

2.3.2 Monotherapy Trials

Luseogliflozin 2.5 mg once daily significantly reduced HbA1c over 24 weeks compared with placebo, in a randomised double-blind phase III trial (JapicCTI111661) in 158 Japanese patients with T2DM. HbA1c levels decreased 0.63 % from baseline in the luseogliflozin group compared with an increase of 0.13 % in the placebo group, with a between group difference of −0.75 % at the end of the study ($p < 0.001$). Stratification of the change in Hb1Ac levels according to baseline values showed that the decrease in Hb1Ac levels was greater in patients with higher Hb1Ac levels at baseline. Luseogliflozin was associated with a significant increase in urinary glucose excretion up to 2 hours after a meal, and a significant decrease in fasting plasma glucose levels compared with placebo ($p < 0.001$). Body weight and abdominal circumference decreased by 2.70 kg and 2.17 cm, respectively by the end of the trial in the luseogliflozin group compared to 0.93 kg and 0.92 cm reductions, respectively, in the placebo group ($p < 0.001$ and $p < 0.5$, respectively) [18, 19].

The efficacy of luseogliflozin was maintained over 52 weeks, as demonstrated in an open-label, long-term phase III trial (JapicCTI111509) in 299 Japanese patients with T2DM. In this trial, the reduction in HbA1c from baseline to the 52 week endpoint was 0.5 % ($p < 0.05$). Luseogliflozin significantly improved postprandial blood glucose levels 2 h after meals, as well as fasting blood glucose levels. Reductions in body weight and abdominal circumference were also observed [18].

Luseogliflozin at a dosage of 1–10 mg once daily for 12 weeks was associated with significant improvements in glycaemic control and reduced body weight in a phase II study in 280 Japanese patients with T2DM. At the study endpoint HbA1c was reduced by 0.51, 0.61, 0.68 and 0.64% relative to placebo in patients treated with luseogliflozin 1, 2.5, 5 and 10 mg/day, respectively (all $p < 0.001$ vs. placebo). Significant reductions in fasting plasma glucose levels (18.7, 24.9, 29.1 and 29.3 mg/dL, respectively; all $p < 0.001$ vs. placebo) and body weight (0.95, 1.45, 2.12 and 2.05 kg, respectively; all $p < 0.001$ vs. placebo) relative to placebo at endpoint were also observed [20].

Once-daily luseogliflozin also significantly reduced HbA1C and body weight in a further phase II trial in 236 Japanese patients with T2DM. Patients were randomised to 12 weeks' luseogliflozin 0.5–5 mg/day or placebo in this double-blind trial. Luseogliflozin produced dose-dependent reductions in HbA1c from baseline (0.42, 0.68 and 0.82 % less than placebo in the 0.5, 2.5 and 5 mg/day groups, respectively, $p < 0.05$ vs. placebo). Significant reductions in fasting plasma glucose and postprandial glucose 2 h after a test meal were also observed relative to placebo group. The 2.5 and 5 mg/day dosages of luseogliflozin were associated with a reduction in body weight of 1.66 and 1.73 kg compared to placebo [21].

2.4 Adverse Events

Luseogliflozin was reported to be well tolerated in phase III monotherapy trials, with most reported adverse events considered to be of mild severity. In a 24-week double-blind trial the overall frequency of adverse effects in patients treated with luseogliflozin was similar to that in placebo recipients (59.5 vs. 57 %, respectively) [18]. 75.3 % of patients who received luseogliflozin in a 52-week open label trial experienced adverse events [18].

In a trial of luseogliflozin as add-on therapy to various other oral antihyperglycaemic drugs the frequency of adverse events, serious adverse events and adverse events leading to discontinuation were similar in all treatment groups. Hypoglycaemia and urinary tract or genital

Clinical trials of luseogliflozin in patients with type 2 diabetes mellitus conducted by Taisho Pharmaceutical

Drugs	Study phase	Status	Study location	Trial identifiers
Luseogliflozin	III	Completed	Japan	JapicCTI111661
Luseogliflozin	III	Completed	Japan	JapicCTI111509
Luseogliflozin + glimepiride	III	Completed	Japan	JapicCTI111507
Luseogliflozin + metformin or a DPP4i or pioglitazone or a glinide or α-GI	III	Completed	Japan	JapicCTI111508
Luseogliflozin	III	Completed	Japan	JapicCTI-111543
Luseogliflozin	II	Completed	Japan	JapicCTI-101191
Luseogliflozin	II	Completed	Japan	JapicCTI-090908

DPP4i Dipeptidyl peptidase-4 inhibitor, *α-GI* α-glucosidase inhibitor

infections were the most notable adverse events and occurred in all treatment groups [17]. In a 52 week trial of luseogliflozin as an add-on to glimepiride the overall incidence of adverse events was 81.3 %, mostly of mild severity. The incidence of serious adverse events and adverse events leading to discontinuation were 6.0 and 2.7 %, respectively. In an initial 24-week double-blind phase the incidence of hypoglycaemia was 8.7 and 4.2 % in the luseogliflozin and placebo groups, respectively. This increased slightly to 10.7 % in patients who received luseogliflozin for 52 weeks; no cases of serious hypoglycaemia were reported. The incidence of mild urinary tract or genital infection, and abnormally frequent urination (pollakiuria) were 2.0 and 2.7 %, respectively, with no serious cases reported [16].

Luseogliflozin was well tolerated in a 12-week double-blind, placebo-controlled, phase II trial in 236 Japanese patients with T2DM. Mild pollakiuria was observed in six patients who received luseogliflozin at a dosage of 2.5 or 5 mg/day. No hypoglycaemia (blood glucose level <70 mg/dL) and no clinically relevant changes in serum creatinine or cystatin C levels were observed [22]. The frequency of adverse events was similar in luseogliflozin 1, 2.5, 5 and 10 mg/day and placebo recipients in a second phase II trial in 280 Japanese patients with T2DM. No major or serious safety concerns were observed in patients treated with luseogliflozin and no episodes of hypoglycaemia (blood glucose level <70 mg/dL) were observed. Eighteen instances of mild pollakiuria or urine output increase were reported in luseogliflozin recipients, all of mild severity [23].

2.5 Ongoing Clinical Trials

No ongoing clinical trials of luseogliflozin are listed on the Taisho, clinicaltrials.gov, World Health Organisation ICTRP or the Japan Pharmaceutical Information Center websites.

3 Current Status

Luseogliflozin received its first global approval on the 24th of March 2014 in Japan for the once-daily treatment of T2DM in adults. It is approved for use as either monotherapy or in combination with other antihyperglycaemic drugs.

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References

1. Abdul-Ghani MA, Norton L, DeFronzo RA. Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. Curr Diabetes Rep. 2012;12(3):230–8.
2. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med. 2013; 159(4):262–74.
3. Taisho P. Acquisition of Manufacturing and Marketing Approval in Japan for SGLT2 Inhibitor Lusefi(Rm) Tablets 2.5 mg and Lusefi(Rm) Tablets 5 mg [media release. http://www.taisho-holdings.co.jp]. 24 Mar 2014.
4. Novartis. Lusefi (luseogliflozin): Japanese prescribing information [In Japanese]. 2014. http://medical.taishotoyama.co.jp/cgi-bin/index2_n.cgi?mode=sel&rows=86&caut=tenp&page=/data/tenp/pdf/tenp_lsf.pdf. Accessed 11 May 2014.
5. Taisho Pharmaceutical Holdings Co L. Signing of Domestic Sales Rights Licensing Agreement Regarding SGLT2 Inhibitor TS-071 [media release]. http://www.taisho-holdings.co.jp. 30 Nov 2012.
6. Kakinuma H, Oi T, Hashimoto-Tsuchiya Y, et al. (1S)-1,5-anhydro-1-[5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl]-1-thio-D-glucitol (TS-071) is a potent, selective sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for type 2 diabetes treatment. J Med Chem. 2010;53(8):3247–61.
7. Teisuke T, Kozakai A, Kojima N, et al. Long-term treatment of TS-071, a novel, potent and selective SGLT2 inhibitor, improves

hyperglycaemia and prevents the loss of beta cell in diabetic mice. Diabetologia. 2011;54:S345.
8. Yamamoto K, Uchida S, Kitano K, et al. TS-071 is a novel, potent and selective renal sodium-glucose cotransporter 2 (SGLT2) inhibitor with anti-hyperglycaemic activity. Br J Pharmacol. 2011;164(1):181–91.
9. Uchida S, Takahashi T, Tomoike H, et al. TS-071, a novel, potent and selective SGLT2 inhibitor, induces weight loss and a reduction in adipocyte size in diet-induced obese rats. Diabetes. 2011;60:A274.
10. Sasaki T, Seino Y, Fukatsu A, et al. Safety, pharmacokinetics, and pharmacodynamics of single and multiple luseogliflozin dosing in healthy Japanese males: a randomized, single-blind, placebo-controlled trial. Adv Ther. 2014;31(3):345–61.
11. Sasaki T, Seino Y, Fukatsu A, et al. TS-071, a novel potent and highly selective renal sodium-glucose co- transporter 2 (SGLT2) inhibitor, increases urinary glucose excretion and reduces plasma glucose levels in Japanese patients with type 2 diabetes mellitus. 47th Annual Meeting of the European Association for the Study of Diabetes. 2011:abstr. 846.
12. Morrow LA, Guttierrez MJ, Tanaka Y, et al. Luseogliflozin (TS-071), a novel, potent, and selective inhibitor of SGLT2 is safe and well-tolerated in type 2 diabetes mellitus and showed dosedependent PK/PD in both US/Japanese ethnicities. Diabetologia. 2012;55:S304.
13. Haneda M, Seino Y, Sasaki T, et al. The effect of luseogliflozin (TS-071), a selective SGLT2 inhibitor, on pharmacodynamics and pharmacokinetics in Japanese type 2 diabetic subjects with renal impairment. Diabetes. 2012;61:A273.
14. Sasaki T, Seino Y, Samukawa Y, et al. Effects of gender and age on the pharmacokinetics and pharmacodynamics of luseogliflozin (TS-071), a selective SGLT2 inhibitor. Diabetes. 2012;61:A275.
15. Nakai Y, Mutoh M. Luseogliflozin (TS-071) a novel, potent and selective sglt2 inhibitor, did not affect the PK of several oral diabetic agents in clinical. Diabetes. 2012;61:A607.
16. Inagaki N, Seino Y, Sasaki T, et al. Luseogliflozin, a selective SGLT2 inhibitor, added on to glimepiride for 52 weeks improves glycaemic control with no major hypoglycaemia in Japanese type 2 diabetes patients. 49th Annual Meeting of the European Association for the Study of Diabetes. 2013:abstr. 184.
17. Haneda M, Seino Y, Sasaki T, et al. Luseogliflozin, a SGLT2 inhibitor, as add-on therapy to 5 types of oral antidiabetic drugs improves glycaemic control and reduces body weight in Japanese patients with type 2 diabetes mellitus. 49th Annual Meeting of the European Association for the Study of Diabetes. 2013:abstr. 957.
18. Seino Y, Sasaki T, Fukatsu A, et al. Luseogliflozin, a selective SGLT2 inhibitor, improves glycemic control as monotherapy in Japanese patients with T2DM. World Diabetes Congress 2013. 2013:abstr. P-1472.
19. Seino Y, Sasaki T, Fukatsu A, et al. Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. Curr Med Res Opin. 2014. doi:10.1185/03007995.2014.912983.
20. Seino Y, Sasaki T, Fukatsu A, et al. Dose-finding study of luseogliflozin in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, double-blind, placebo-controlled, phase II study. Curr Med Res Opin. 2014. doi:10.1185/03007995.2014.909390:1-14.
21. Seino Y, Sasaki T, Fukatsu A, et al. TS-071, a Novel and Selective SGLT2 Inhibitor, Improved Glycemic Control and Decreased Body Weight in 12-Week Study of Japanese Patients with Type 2 Diabetes Mellitus. 71st Annual Scientific Sessions of the American Diabetes Association. 2011:abstr. 0998-P.
22. Seino Y, Sasaki T, Fukatsu A, et al. TS-071, a novel and selective SGLT2 inhibitor, improved glycemic control and decreased body weight in 12-week study of Japanese patients with type 2 diabetes mellitus. Diabetes. 2011;60:A274.
23. Seino Y, Sasaki T, Fukatsu A, et al. Luseogliflozin (TS-071), a selective SGLT2 inhibitor, improves glycaemic control and lowers body weight in a 12-week study in Japanese patients with type 2 diabetes mellitus. 48th Annual Meeting of the European Association for the Study of Diabetes. 2012:abstr. 740.