

# The journey from gene knockout to clinical medicine: telotristat and sotagliflozin

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**Abstract:** Gene knockout has been a powerful technique to evaluate the physiologic role of selected gene products. Lexicon pioneered high-throughput gene knockout technology and went further in designing agents to inhibit products of gene expression. Two agents have entered late-stage development. Telotristat is an inhibitor of tryptophan hydroxylase (TPH), preventing the production of serotonin. Although this agent blocks the two isoforms of TPH, it does not cross the blood–brain barrier, thus avoiding central neurologic manifestations. It inhibits the peripheral production of serotonin, and in particular prevents serotonin action in the intestines, resulting in decreased peristaltic action. Lexicon successfully developed telotristat to treat carcinoid syndrome not responding adequately to somatostatin inhibitors. Sotagliflozin development proceeded from the observation that dual inhibition of SGLT2 in the kidneys and SGLT1 in the intestines resulted in increased renal glucose excretion, reduced early-phase glucose absorption, as well as increased blood levels of GLP-1 and PYY. Initial development efforts focused on type 1 diabetes and have shown reduced postprandial glucose levels, less tendency to hypoglycemia, and lower HbA1c. Several other SGLT2 inhibitors have been associated with increased frequency of diabetic ketoacidosis (DKA). In the type 1 trials, sotagliflozin-treated individuals experienced DKA at a higher rate than placebo-treated patients. The sotagliflozin development program has now been extended to trials on type 2 diabetes. Long-term clinical trials will determine the benefits and risks of the agent in comparison to other currently marketed SGLT2 inhibitors.

**Keywords:** gene knockout models, telotristat, SGLT1, SGLT2, diabetic ketoacidosis, sotagliflozin

## Introduction

The story of Lexicon Pharmaceuticals illustrates the successful application of a new approach to scientific discovery and development of new therapeutic agents. The company was originally established to pursue high-throughput knockout genomic biology. This innovative science led to the underlying concept that the normal products of gene expression are not necessarily beneficial in all conditions. It was considered that reduction of expression of certain genes might be desirable in certain situations. At the time Lexicon began operations, the effects of modification of individual genes were assessed by gene targeting.<sup>1</sup> This technique introduced sequence variations at known genes, typically by sequential homologous recombination and breeding manipulation. Lexicon initially targeted a number of pre-specified genes to create gene knockout mice. The effects of knockout of specific genes were then assessed in the mouse colonies. This conventional gene-targeting approach was later replaced by a comprehensive gene-trapping technology using a gene trap vector to randomly introduce a DNA element including a tag sequence into endogenous genes.<sup>2</sup> Unlike gene targeting by

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homologous recombination, a single gene trap vector can be used to mutate thousands of individual genes and efficiently produce sequence tags for the rapid identification of the alleles which have been altered. Lexicon built an extensive library of over 350,000 mutated embryonic stem cells with 9,000 genes affected. They carefully studied the effects of knockout of individual genes to discover potentially beneficial effects. For those gene mutations which showed therapeutic potential, they then designed agents to inhibit the gene product of interest. This was a new and different approach to discovery of therapeutic agents. Lexicon has successfully developed two agents using this technology. The first was telotristat, a tryptophan 5-hydroxylase inhibitor that reduces serotonin synthesis, developed as a treatment for carcinoid diarrhea not adequately controlled on somatostatin inhibitors. The second agent brought forward was sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, to treat diabetes.

## Telotristat and the carcinoid syndrome

Well-differentiated neuroendocrine tumor (NET), formerly known as carcinoid tumor, arises from cells of the neuroendocrine system and may secrete hormones and vasoactive substances. The main hormone responsible for symptoms is 5-hydroxytryptophan (serotonin), although there is also a contribution by other NET hormones such as histamine, bradykinin, prostaglandins, and substance P.<sup>3</sup> Common sites of origin include the gastrointestinal (GI) tract, the pancreas, and the lung. GI tumor products route through the portal vein into the liver and are metabolized, so that symptoms become manifest only when liver metastases release their secretions into the systemic circulation. The symptoms of carcinoid syndrome include flushing, severe diarrhea, abdominal pain, wheezing, and valvular heart disease.<sup>3</sup> Uncontrolled diarrhea can lead to malabsorption, electrolyte depletion, weight loss, malnutrition, and dehydration. The occurrence of carcinoid heart disease is directly related to circulating levels of serotonin.<sup>4</sup>

Serotonin is a brain neurotransmitter but also acts as a paracrine messenger in the gut, being involved in peristaltic and secretory reflexes.<sup>5</sup> Carcinoid symptoms can be quite severe, with diarrhea limiting normal activity. The mainstay of treatment is somatostatin inhibition.<sup>6</sup> Octreotide suppresses secretion by neuroendocrine cells, but it has to be given frequently. Long-acting somatostatin inhibitors such as sustained-release octreotide and lanreotide are used for maintenance care. However, results are often incomplete and there is tachyphylaxis.<sup>7</sup>

Serotonin is formed by enzymatic hydroxylation by the enzyme tryptophan hydroxylase (TPH). TPH was found to have two isoforms.<sup>8</sup> TPH2 is active in the brain and in the myenteric plexus.<sup>9</sup> Serotonin has a beneficial effect in depression, illustrated by the therapeutic benefit of selective serotonin reuptake inhibitors.<sup>10</sup> TPH1 is distributed in the periphery, in particular in the GI system.<sup>11</sup> Lexicon developed selective knockout models for TPH1 alone and for TPH2 alone and double-knockout colonies with both TPH1 and TPH2 deleted.<sup>12</sup> In TPH2 knockout and TPH1/TPH2 double-knockout animals, brain serotonin levels were markedly reduced while intestinal levels were normal. Conversely, intestinal levels were significantly lower in TPH1 knockout animals. Surprisingly, despite the widespread distribution of serotonin receptors, the animals were not overtly impaired.<sup>13</sup> It was possible to demonstrate behavioral changes on a battery of testing procedures in the TPH2 and TPH1/TPH2 knockouts. Conversely, TPH1 knockout animals performed normally on behavioral testing, but had reduced fecal propulsion in the intestines.<sup>14</sup> The reduction in fecal propulsion suggested a possible beneficial effect in carcinoid syndrome patients suffering from unremitting diarrhea. Para-chlorophenylalanine, an inhibitor of TPH, has been evaluated in the past as a treatment for carcinoid syndrome, but this agent induced depression in patients, presumably due to reduction in brain serotonin.<sup>15</sup>

Lexicon used a high-throughput binding assay for TPH1 to identify compounds with high selectivity for this enzyme.<sup>16</sup> They screened a library of 200,000 agents to choose a candidate for further drug development. They eventually selected telotristat ((2S)-2-amino-3-[4-[2-amino-6-[(1R)-1-[4-chloro-2-(3-methylpyrazol-1-yl)phenyl]-2,2,2-trifluoroethoxy]pyrimidin-4-yl]phenyl]propanoate).<sup>17</sup> Telotristat is not selective for TPH1. It shows equivalent binding to TPH1 and to TPH2 but does not cross the blood–brain barrier. Telotristat is formulated as the ethyl ester prodrug as a hippurate salt. In *in vitro* studies using purified human enzymes, telotristat ethyl and telotristat inhibited TPH1 and TPH2. The inhibitory potency of telotristat was about 28- and 34-fold greater for TPH1 and TPH2, respectively, compared to the parent drug, telotristat ethyl.<sup>17</sup>

## Clinical pharmacokinetics

After oral absorption, the peak plasma concentrations of telotristat ethyl and its active metabolite, telotristat, were achieved within 0.5–2 hours and within 1.5–3 hours, respectively. Telotristat ethyl was extensively metabolized to its active metabolite, telotristat, by carboxylesterases.

The systemic exposure to telotristat was about >300-fold higher than that of telotristat ethyl and increased in a dose-proportional manner in the range of 100–1,000 mg under fasted conditions. Peak plasma concentrations of telotristat ethyl were achieved within 0.5–2 hours, and those of telotristat within 1–3 hours. Thereafter, plasma concentrations declined in a biphasic manner. Following multiple-dose administrations of telotristat ethyl 500 mg three times daily (TID), there was no significant accumulation at steady state for both telotristat ethyl and telotristat.<sup>18</sup>

Lexicon chose carcinoid syndrome as the first possible indication for telotristat. Prevalence rates of NETs have been estimated at ~103,312 cases in the US in 2004.<sup>19,20</sup> Somatostatin analogs (SSAs; octreotide and lanreotide) are the first-line therapy for carcinoid syndrome, working by inhibiting the release of serotonin and other bioactive substances produced by NETs to produce symptomatic relief.<sup>21,22</sup> There is also a reduction in tumor growth. Patients often have decreasing response to SSAs over time resulting in resurgence of symptoms including diarrhea and flushing. Sixty percent of patients stop responding after 3 months of octreotide treatment.<sup>23</sup> This may be due to an increase of metastatic tumor cells or a decrease in cell surface receptors.

## Clinical studies of telotristat

There were two multicenter placebo-controlled, randomized double-blind pivotal trials of telotristat in patients with carcinoid syndrome.<sup>18</sup> LX301 (TELESTAR) and LX303 (TELECAST) enrolled adult patients with well-differentiated metastatic NETs and carcinoid syndrome. LX301 required patients to have a documented history of carcinoid syndrome with at least four bowel movements (BMs) per day, and to have been treated with a stable dose of SSA for at least 3 months. The primary efficacy end point in LX301 was change in frequency from the baseline number of daily BMs averaged over the 12 weeks of treatment. LX303 broadened the study to patients with documented carcinoid syndrome without the above requirements. The primary efficacy end point in LX303 was the pharmacodynamic effect of telotristat ethyl as measured by percent change from baseline in the 24-hour urinary 5-HIAA levels at week 12.<sup>18</sup> Secondary end points included frequency of BMs.

There were 135 patients enrolled in LX301 and 76 in LX303 (N=76), randomized 1:1:1 to telotristat ethyl 250 mg TID, telotristat ethyl 500 mg TID, or placebo. Both doses of telotristat ethyl significantly reduced BM frequency vs placebo in both studies. Reductions from baseline of approximately two BMs per day were observed in LX301.<sup>24–26</sup>

Both studies demonstrated statistically significant reductions in urinary 5-HIAA at both doses of telotristat ethyl. Patients treated with telotristat gained weight.<sup>27</sup> There was no significant difference in flushing or abdominal pain. Abdominal pain and nausea were common complaints occurring in approximately a third of the patients, possibly related to slowing of gastric motility. Constipation was reported by two (3%), four (6%), and five (7%) patients in the placebo, telotristat ethyl 250 mg TID, and telotristat ethyl 500 mg TID treatment groups, respectively.

Although telotristat does not cross the blood–brain barrier, there was a numerical imbalance in the incidence of depression in the telotristat ethyl 500 mg TID treatment group and telotristat ethyl 250 mg TID treatment group compared with the placebo-controlled safety population. These events were reported by the investigators as mild or moderate in intensity and generally did not limit treatment. Other adverse events (AEs) in the studies reflected the seriousness of the underlying metastatic disease involving the liver. After review of the study results, the US Food and Drug Administration and the European Union approved telotristat which is now marketed for patients with carcinoid syndrome not responding adequately to SSAs.

## Sotagliflozin and diabetes

Glucose transport across cell membranes is mediated by a family of glucose transport proteins, the facilitative glucose transport proteins (GLUT), and the sodium ATP-energized SGLTs.<sup>28</sup> The SGLT proteins are expressed differentially in various tissues. SGLT1 is widely expressed in various tissues and has a primary role in the brush border of the intestines to absorb glucose from the gut.<sup>29</sup> It also has a lesser effect in the kidney to reabsorb glucose from the renal tubules. SGLT2 has a more narrow tissue expression profile and has the primary role of reabsorption of glucose from the renal tubules.<sup>30</sup> Lexicon developed knockout models of SGLT2 which exhibited a substantial increase in urinary glucose excretion (UGE) and lower fed and fasting glucose levels when compared to normal littermate mice. Humans with deficient SGLT1 suffer from glucose–galactose malabsorption.<sup>31</sup> Consequently, pharmaceutical companies were reticent to pursue SGLT1-inhibitory agents. Lexicon homozygous SGLT1 knockout mice maintained on a diet containing glucose and galactose exhibited unformed or watery stools, decreased food intake, and reduced weight gain. However, Lexicon went further in interbreeding to create mice heterozygous for the SGLT1 mutation. These animals had normal stools, food intake, and weight gain, and postprandial glucose (PPG)

levels were markedly reduced.<sup>32</sup> Intestinal L cells exposed to high glucose and fatty acid concentrations secrete GLP-1 and PYY, a satiety hormone.<sup>33</sup> The heterozygous SGLT1 knockout animals had increased delivery of glucose to the distal small intestine and cecum, with increased GLP-1. Lexicon cross bred SGLT2 and SGLT1 knockout animals. Under normal physiologic conditions, between 83% and 98% of filtered glucose is reabsorbed by active transport in the proximal convoluted tubule, and almost all of the remaining glucose is actively transported later, largely in the proximal straight tubule.<sup>34</sup> In the kidney, SGLT2 has the dominant role in mediating glucose reabsorption, largely in the proximal convoluted tubule. SGLT1 contributes about 10% to urinary glucose reabsorption mainly in the proximal straight tubule. In comparisons of the various strains, the investigators found that in the SGLT2 knockout mice with intact SGLT1, glucose reabsorption still attained 40%–50% of the normal level, suggesting increased compensatory SGLT1-mediated effect.<sup>35</sup> These original studies led to a better understanding of the comparative roles of SGLT1 and SGLT2 in renal handling of glucose and suggested that complete SGLT2 inhibition at the kidney with only partial SGLT1 inhibition in the intestines might exert a potent effect on glucose levels without triggering undesirable GI side effects.

As a result of these findings, Lexicon decided to synthesize agents to inhibit both SGLT2 and SGLT1. A number of different pharmaceutical companies have developed currently marketed SGLT2 inhibitors. Canagliflozin from Johnson & Johnson, dapagliflozin from Bristol-Myers, empagliflozin from Boehringer Ingelheim, and ertugliflozin from Merck were products of conventional drug development programs. Lexicon produced a number of compounds with dual inhibitory effects on SGLT1 and SGLT2.<sup>36</sup> Sotagliflozin ((2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio) tetrahydro-2H-pyran-3,4,5-triol), an orally available small molecule, was one of the agents synthesized.<sup>36</sup> The IC<sub>50</sub> of sotagliflozin for human SGLT1 is 36 nM and is 1.8 nM for human SGLT2. Sotagliflozin is 20 times more potent as an inhibitor of SGLT2 than of SGLT1 at the kidney but still possesses significant activity as an inhibitor of intestinal SGLT1. The other glucose transport inhibitors are much more selective. In comparison, canagliflozin is 200 times more potent in suppression of SGLT2 than SGLT1.

## Pharmacokinetics and pharmacologic actions

In both short- and long-term studies in mice, rats, and dogs, there was a marked increase in UGE and reduced glucose

elevation during oral glucose tolerance tests (OGTTs).<sup>37</sup> As a result of the inhibition of SGLT1 and subsequent reduced glucose absorption in the GI tract, sotagliflozin treatment led to increases in intestinal glucose and decreases in the pH of cecal contents in both diet-induced obese mice and in hybrid lean mice. These changes led to a significant increase in postprandial GLP-1 and PYY levels and lower glucose excursions during OGTTs.<sup>32,38</sup> In non-obese diabetic mice, a model of type 1 diabetes, sotagliflozin significantly improved glycemic control and reduced the daily insulin requirement.<sup>39</sup> In human subjects, absorption of sotagliflozin was rapid with detectable plasma concentrations observed within 15 minutes post-dosing with single and multiple doses of 150 and 300 mg in a liquid formulation.<sup>37</sup> The mean  $\pm$  SD values for t<sub>1/2</sub> (half-life) were 20.7 $\pm$ 13.7 and 13.5 $\pm$ 5.3 hours in the 150 and 300 mg dose groups, respectively. Steady-state levels of sotagliflozin were observed after 14 days of dosing.

## Clinical studies

In an initial dose-finding 12-week study in type 2 metformin-treated patients, there was a reduction in HbA<sub>1c</sub> (0.09%, placebo; 0.42%, 75 mg/day; 0.52%, 200 mg/day; 0.80%, 200 mg twice daily; 0.92%, 400 mg/day).<sup>40</sup> SBP decreased (–5.7 mm Hg), as did weight (–1.85 kg). At a dose of 400 mg daily, sotagliflozin significantly inhibited SGLT2 and intestinal SGLT1, but the blood levels were insufficient to have a measurable effect on renal SGLT1. Yet, reductions in PPG were significant even in patients with stage 3B renal impairment (glomerular filtration rate 30–44 mL/min), suggesting a benefit mediated primarily by SGLT1 inhibition in the intestines.<sup>41</sup> In this initial study, primarily on type 2 diabetes, there were no significant safety concerns.

All the SGLT2 inhibitors to date have been developed and marketed to treat type 2 diabetes. Lexicon made the decision to target type 1 diabetes as their first therapeutic indication for sotagliflozin. Impairment of endogenous insulin secretion in diabetes leads to inability to respond rapidly to ingestion of carbohydrates. As a result, there is an increase in PPG levels after a meal, particularly exaggerated in type 1 diabetes where there is a near-total absence of endogenous insulin secretion.<sup>42</sup> Insulin injections are typically given prior to a meal and will acutely raise serum insulin levels, but subcutaneous insulin creates a repository which lasts well beyond meal disposal, risking hypoglycemia at later times. The effect of SGLT inhibition is independent of insulin action. SGLT2 inhibitors have been studied in type 1 diabetes, but the potential advantage of sotagliflozin was its dual action, that is, increase in excretion of blood glucose in the urine and suppression of the absorption of intestinal glucose.



**Table 1** The three pivotal sotagliflozin studies

Study	Number of patients	Sotagliflozin dosage	Placebo-adjusted A1c reduction	Severe hypoglycemia	DKA
inTandem 1	793	200 mg, 400 mg, or placebo	0.25% (200 mg)** 0.31% (400 mg)**	9.7% (placebo) 6.5% (200 mg) 6.2% (400 mg)	0.4% (placebo) 3.4% (200 mg) 4.2% (400 mg)
inTandem 2	781	200 mg, 400 mg, or placebo	0.37% (200 mg)** 0.35% (400 mg)**	5% (placebo) 5% (200 mg) 2.3% (400 mg)	0% (placebo) 0.4% (200 mg) 1.1% (400 mg)
inTandem 3	1,402	400 mg or placebo	0.46% (400 mg)**	3.0% (placebo) 2.4% (400 mg)	0.6% (placebo) 3.0% (400 mg)

**Note:** \*\* $P < 0.01$ .

**Abbreviation:** DKA, diabetic ketoacidosis.

There have been three large pivotal placebo-controlled trials (inTandem) in type 1 diabetes patients with HbA1c of 7%–11% on either conventional multiple daily dose injections or insulin pump treatment (Table 1). The design of these studies incorporated a pre-randomization period of 6 weeks to allow optimization of insulin treatment after which the insulin regimen was to be kept constant. Patients were highly educated as to potential symptoms of diabetic ketoacidosis (DKA) and were provided  $\beta$ -hydroxybutyrate home testing to detect incipient ketosis. InTandem 1 was conducted in the US and Canada.<sup>43</sup> InTandem 2 was a European study.<sup>44</sup> The inTandem 1 patients treated with sotagliflozin had a mean placebo-corrected A1c reduction from baseline of 0.25% on 200 mg of sotagliflozin taken once daily and a reduction of 0.31% on 400 mg.<sup>43</sup> For InTandem 2, the placebo-adjusted reduction was 0.37% in the 200 mg dose arm ( $P < 0.001$ ) and 0.35% in the 400 mg dose arm ( $P < 0.001$ ).<sup>44</sup> The incidence of treatment-emergent AEs was similar in the three groups for both InTandem studies. There were less severe hypoglycemic events in the 400 mg dose arms, and there were more patients with DKA events in the two sotagliflozin dose arms (Table 1).

Lexicon chose the 400 mg dose for the final pivotal study (InTandem 3), enrolling 1,402 patients with type 1 diabetes on either insulin pump or multiple daily insulin injections.<sup>45</sup> The least-squares mean change from baseline was significantly greater in the sotagliflozin group than in the placebo group for HbA1c (difference,  $-0.46$  percentage points), weight ( $-2.98$  kg), SBP ( $-3.5$  mmHg), and mean daily bolus dose of insulin ( $-2.8$  units per day) ( $P \leq 0.002$  for all comparisons). The rate of documented hypoglycemia was significantly lower in the sotagliflozin group than in the placebo group, but the rate of DKA was higher in the sotagliflozin group (3.0%, 21 patients) than in the placebo group (0.6%, four patients). DKA led to discontinuation of 11 sotagliflozin patients. There were 24 serious acidosis-related events in sotagliflozin-treated patients compared to five in placebo patients. In addition, there were 39 acidosis

events classified as non-severe in the sotagliflozin cohort compared to only 12 in the placebo group. Other AEs of special significance included genital mycotic infections occurring in 6.4% of the sotagliflozin group and 2.1% of the placebo patients. Diarrhea was more frequent in the sotagliflozin patients (4.1%) than in the placebo patients (2.3%), perhaps reflecting the GI effect of SGLT1 inhibition.

## Conclusion

The gene knockout approach to drug discovery is a major innovation. Standard animal husbandry with careful characterization of knockout mice has led to conceptual breakthroughs in the treatment of carcinoid syndrome and potentially of type 1 diabetes. In both the telotristat and the sotagliflozin programs, findings in the gene knockout animals led to a better understanding of the physiology of the processes studied. It is now appreciated that serotonin has different receptors both in the central nervous system and the GI tract. Inhibition of GI receptors does not promote depression.

The underlying hypothesis is that reduction of normal gene expression products may be beneficial in certain conditions. Despite the ubiquitous role of serotonin as a neurologic messenger, the deletion of TH1 receptors did not result in severe impairments in these knockout animals. In fact, the changes in intestinal propulsion were relatively limited. Although a suitable agent to suppress TH1 selectively was not found, telotristat did not cross the blood–brain barrier and consequently did not exacerbate depression. It has proven benefit in carcinoid diarrhea and is now marketed for patients with inadequate response to somatostatin agonists.

The extensive studies of SGLT2 and SGLT1 knockouts and combined heterozygotes provided a clear understanding of the comparative roles of these two glucose transport proteins in the kidney. Sotagliflozin is effective in inhibition of both SGLT1 and SGLT2. It has a beneficial effect in promoting glucose excretion in the kidneys and also in

suppressing glucose absorption in the intestines. The SGLT1 inhibitory effect in the intestines leads to an increase in GLP-1. As a result of these dual effects, the promise of sotagliflozin is to obtain the benefits of both SGLT2 inhibition and GLP-1 agonist action.

Lexicon chose type 1 diabetes as their initial indication for development. In the first two large sotagliflozin Phase III trials, it is notable that there were significantly more cases of DKA in the sotagliflozin arms than in the placebo groups. In these studies, investigators and patients were highly educated to look for the signs and symptoms of DKA. Patients were asked to perform ketone monitoring throughout the study. The incidence of DKA on the 200 mg dose level of sotagliflozin was lower than at the 400 mg level, and there was no clear superiority of the higher dose in terms of reduction of HbA1c or of hypoglycemic events. In retrospect, it may have been preferable to utilize a 200 mg dose for the third definitive trial in Tandem 3. In that third trial, although there were DKA events in the placebo group, there were significantly more cases in sotagliflozin-treated subjects. In addition, there were more acidosis events. On the positive side, hypoglycemia with documented glucose <55 mg/dL was reduced by sotagliflozin treatment in all three in Tandem studies.

Recently, results of the Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (DEPICT) study of the selective SGLT2 inhibitor dapagliflozin and the Empagliflozin as Adjunctive to insulin therapy (EASE) study of empagliflozin in type 1 diabetes patients were released.<sup>46,47</sup> The placebo-adjusted reduction in HbA1c was 0.33% for 5 mg and 0.36% for 10 mg dapagliflozin. Although hypoglycemic events were comparable across treatment groups, more patients in the dapagliflozin groups had events adjudicated as definite DKA (4.0%, 3.4%, and 1.9% in dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively). Results of the two EASE studies also demonstrated HbA1c reductions of -0.28% (95% CI, -0.42 to -0.15) for 2.5 mg, -0.54% (95% CI, -0.65 to -0.42) for 10 mg, and -0.53% (95% CI, -0.65 to -0.42) for 25 mg (all  $P < 0.0001$ ). Empagliflozin 2.5/10/25 mg doses, respectively, reduced mean weight by -1.8/-3.0/-3.4 kg (all  $P < 0.0001$ ), increased glucose time-in-range by +1.0/+2.9/+3.1 h/day ( $P < 0.0001$  for 10 and 25 mg), lowered total daily insulin dose by -6.4%/-13.3%/-12.7% (all  $P < 0.0001$ ), and decreased SBP by -2.1/-3.9/-3.7 mmHg (all  $P < 0.05$ ). There was a higher incidence of genital infections on empagliflozin. Adjudicated DKA occurred more with empagliflozin 10 mg (4.3%) and 25 mg (3.3%) but

was comparable between empagliflozin 2.5 mg (0.8%) and placebo (1.2%) in the initial 26 weeks of the study.

Lexicon pursued an initial indication of type 1 diabetes. There are certainly potential benefits for these patients in modest improvements in glycemic control. There appears to be less variability of glucose levels on sotagliflozin as well as the pure SGLT2 inhibitors dapagliflozin and empagliflozin. There may be less severe hypoglycemia with these adjunctive treatments. Yet, the sotagliflozin, dapagliflozin, and empagliflozin studies have clearly established a tendency for SGLT2 inhibitors to promote DKA. As a result, it may be difficult to obtain marketing approval for these agents in type 1 diabetes due to the increased incidence of DKA, which is, of course, a very serious condition.

An additional concern with the use of SGLT2 inhibitors and sotagliflozin in type 1 diabetes is the lack of information on the risk in pregnancy. There are no published data on the teratogenic potential of sotagliflozin. Type 1 diabetes is predominantly a disease of young people. Young women with type 1 diabetes who are contemplating pregnancy are encouraged to seek strict control of blood glucose to minimize the risk of birth defects. Tight glycemic control in the first trimester and continuing throughout pregnancy is required to avoid maternal, fetal, and neonatal complications.<sup>48</sup> If sotagliflozin arrives on the market, there will be a number of women in childbearing years who will be taking this agent to attain optimal glucose control prepregnancy. However, if sotagliflozin is contributing to improved glycemic control, it would be harmful to the pregnancy to stop this drug abruptly after conception. Yet, we have no data on possible teratogenic risks. DKA during pregnancy is life-threatening with a high rate of fetal loss.<sup>49</sup> It is unknown whether the tendency for sotagliflozin to promote DKA could be increased in the pregnant state.

The future of sotagliflozin may rest in type 2 diabetes. Sanofi has partnered with Lexicon in developing an extensive program to assess sotagliflozin treatment in type 2 diabetes. Sotagliflozin is being evaluated in 11 Phase III studies in T2DM, including a direct head-to-head comparison with empagliflozin, studies on renal impairment, and long-term cardiac outcome trials. Unquestionably, the primary consideration in the evaluation of sotagliflozin in type 2 diabetes patients will be the impact of the agent on cardiovascular events. The long-term studies will clearly be compared to the significant reductions in mortality seen with the pure SGLT2 inhibitor empagliflozin in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) trial<sup>50</sup> and the GLP-1 benefits demonstrated with liraglutide in the Liraglutide Effect and

Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study.<sup>51</sup> The EMPA-REG study of the pure SGLT2 inhibitor empagliflozin in type 2 diabetes has profoundly influenced our approach to treatment of type 2 diabetes. In that study, empagliflozin reduced all-cause mortality (relative risk [RR] of death, 0.69; 95% CI, 0.58–0.82) and cardiovascular mortality (RR, 0.62; 95% CI, 0.50–0.78) in patients with established cardiovascular disease when compared with placebo. In the LEADER trial of the GLP-1 agonist liraglutide, cardiovascular death was reduced (HR, 0.78; 95% CI, 0.66–0.93;  $P=0.007$ ) as well as all-cause mortality (HR, 0.85; 95% CI, 0.74–0.97;  $P=0.02$ ) when compared to placebo.

The Lexicon approach to drug design and development through observation of gene knockout characteristics was unique. The discovery of two isoforms of TPH led to the design of telotristat, a successful therapy for carcinoid diarrhea, which not a common condition, is a significant problem for a small number of patients. Clinical research studies pursuing broader potential indications such as irritable bowel syndrome offer a possibility for much wider eventual use.

In the case of sotagliflozin, the decision to pursue dual inhibition of two gene products was daring as was the pursuit of type 1 diabetes as the primary target of the agent. It now remains for conventional clinical research to evaluate the use of sotagliflozin in the treatment of diabetes.

## Disclosure

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