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An evaluation of US patent 2015065565 (A1) for a new class of SGLT2 inhibitors for treatment 1 of type II diabetes mellitus

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Abstract

Introduction—Type 2 diabetes mellitus (T2DM) is a growing and serious global health problem. Pharmacological inhibition of the sodium–glucose cotransporter-2 (SGLT2; SLC5A2) increases urinary glucose excretion, decreasing plasma glucose levels in an insulin-independent manner. Agents that inhibit SGLT2 have recently become available for clinical therapy of T2DM.

Areas covered—The patent claims a new class of SGLT2 inhibitors: derivatives of dioxa-bicyclo[3.2.1]octane-2,3,4-triol (including ertugliflozin; PF-04971729). The invention describes the design, synthesis and pharmacological tests related to ertugliflozin, which could ultimately lead to efficacious therapy for T2DM alone or in combination with other anti-diabetic agents.

Expert opinion—Ertugliflozin is likely to be of great clinical significance in the near future. Continued analysis of ertugliflozin derivatives to now validate safe and efficacious treatment of T2DM in a larger number of clinical subjects over an extended period is needed to further support clinical utility. Identification, and discussion, of likely contra-indications is also needed.

Keywords

clinical therapy; diabetes; dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives; ertugliflozin; inhibitors; PF-04971729; sodium–glucose linked co-transporter; type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) continues to be clinically challenging despite the numerous therapeutic options available [1]. T2DM is characterized by loss of responsiveness to circulating insulin in muscle and liver tissues that results in sustained high blood glucose levels. Metformin, a biguanide, is currently recommended as first-line therapy for T2DM [2]. However, the progressive nature of T2DM and its side effects mean most patients need additional therapy, for example, glipizide [3]. Unfortunately, insulin secretagogues like glipizide pose additional side effects, such as hypoglycemia, which limit

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Declaration of interest

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their usefulness as therapeutics without close monitoring of glucose levels [4]. Thus, there is a need for additional therapy options that are easy for patients to self-administer and monitor.

The kidney plays an important role in glucose homeostasis and has become a target for therapeutic treatment of diabetes. The kidney contributes to the regulation of glucose homeostasis via at least three mechanisms: most importantly, glucose reabsorption from glomerular filtrate, release of resorbed glucose into the circulation, and also uptake of glucose from the circulation for its own energy needs. The majority of glucose reabsorption from glomerular filtrate is mediated via an electrogenic plasma membrane transporter called sodium–glucose cotransporter 2 (SGLT2, also known as SLC5A2 [solute carrier family 5 member 2]) that is highly expressed in the brush border of renal proximal tubules.

SGLT2 inhibitors can block 90% of renal glucose reabsorption, thereby accentuating urinary glucose excretion, glucosuria [5]. Urinary excretion of excess glucose decreases blood glucose levels, hepatic storage of glucose and insulin secretion. Selective inhibition of SGLT2 is predicted to normalize plasma glucose by enhancing urinary glucose excretion. Consequently, inhibition of SGLT2 activity is a novel and promising treatment for diabetes under late-stage clinical development. There are several US FDA-approved SGLT2 inhibitors, and other agents in advanced stages of clinical development such as dapagliflozin [6,7], canagliflozin [8,9], empaglifozin [10,11]. The patent US 2015065565 (A1) reported a new class of highly selective inhibitors of SGLT2, the dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives (including ertugliflozin; PF-04971729; Pfizer Inc.).

2. Results

The current patent reports on the pharmaceutical compositions and uses of ertugliflozin and its derivatives as inhibitors of the SGLT, and in particular, SGLT2 [12]. These compounds are proposed for the treatment of diseases, conditions and/or disorders mediated by SGLT2. The major scientific findings of the inventors are summarized to two parts: i) those in the patent; and ii) published findings from the same team.

The scientific findings in the patent include:

- Two formulae for ertugliflozin and their syntheses are described, as ertugliflozin exists in different stereoisomeric forms with asymmetric or chiral centers that can be purified by HPLC.
- Ertugliflozin (it is claimed) has a 2000-fold increase in selectivity for human SGLT2 over SGLT1 (IC50: SGLT2 = 0.877 nM vs SGLT1 = 1960 nM) *in vitro* [13,14].
- Ertugliflozin is claimed to be especially useful for treating diseases or conditions that can be ameliorated by inhibition of SGLT2. The pharmaceutical composition comprises a therapeutically effective amount of ertugliflozin.
- Diseases or conditions that can be ameliorated by inhibition of SGLT2 include: Type II diabetes, diabetic nephropathy, insulin resistance syndrome,

hyperglycemia, hyperinsulinemia, hyperlipidemia, impaired glucose tolerance, obesity (including weight control or weight maintenance), hypertension and reducing the level of blood glucose. Ertugliflozin can also be used for treating analogous diseases or conditions in animals.

- Ertugliflozin may be co-administered with other pharmaceutical agents, either as: i) a single pharmacotherapeutic composed of ertugliflozin and at least one other active agent; or ii) two separate pharmacotherapeutics, the first being ertugliflozin, and a second comprising at least one additional active agent.

Published findings from the same team include:

- Ertugliflozin is rapidly absorbed in preclinical species after oral administration, and it is characterized by low clearance (excreted in the urine in preclinical species) and a moderate steady-state distribution volume. There is low potential for pharmacokinetic interaction of ertugliflozin [14].
- Ertugliflozin is well absorbed in humans and eliminated largely via glucuronidation [13].
- Ertugliflozin improved glycemic control, body weight and blood pressure in patients with T2DM suboptimally controlled by metformin, and is well-tolerated [15].

3. Expert opinion

Several SGLT2 antagonists have been identified, including hydrolyzable *O*-glucosides (e.g., phlorizin), and several non-hydrolyzable antagonists, including *O*-glycosides (e.g., sergliflozin, remogliflozin [16]). However, these antagonists were associated with degradation by glucosidase enzymes in the gut and needed to be administered as prodrugs, or parenterally [17], and clinical trials were abandoned. Susceptibility to glucosidase degradation was overcome by the discovery of *C*-glycosides such as dapagliflozin [6,7] and canagliflozin [8,9], with increased lipophilicity and molecular weight [18]. Additionally, several *C*-glycosides induce chromosome breaks and/or gain or loss of function *in vitro* (micronucleus test) [19], with the caveat that *in vitro* data may not be replicated *in vivo* [20]. These non-hydrolyzable antagonists are being, or have been, tested to counteract Type II diabetes in mice [8,21,22] and humans [23]. Thus, until recently, the primary structures of SGLT2 antagonists have been dominated by the *O*-glycosides and *C*-glycosides.

Ertugliflozin, incorporating a structurally novel dioxa-bicyclo-[3.2.1] octane ring system, and derivatives form a third class of potent and selective SGLT2 antagonists, and are described in this patent. The patent team recently published a paper claiming that ertugliflozin is rapidly absorbed in preclinical species after oral administration, and it is characterized by low (urinary) clearance, a moderate steady-state distribution volume and low potential for pharmacokinetic interactions [14,15]. However, no data has been reported showing that ertugliflozin has greater efficacy, duration of action, or drug–drug interactions of ertugliflozin compared to *O*- or *C*-glycosides at this time. Nonetheless, ertugliflozin is less susceptible to glucosidase degradation, less lipophilicity than *C*-glycosides (with

resultant implications in terms of pharmacokinetics and/or safety) [19], and is eliminated largely via glucuronidation [13,14].

The ideal anti-diabetes drug is one that: robustly reduces HbA1c levels, is well tolerated, can be administered easily with low or no risk of hypoglycemia, has good long-term safety, and has added benefits such as a favorable impact on β-cell function, blood pressure, weight and albuminuria. Since ertugliflozin does not rely on exogenous or endogenous insulin to reduce blood glucose levels [24], it has the potential to provide improved long-term glycemic control relative to insulin-dependent oral anti-diabetic agents. Ertugliflozin has been studied in a dose-ranging efficacy and safety study in patients with T2DM [15]. The efficacy of ertugliflozin for 12 weeks on reduction of HbA1c is similar to sitagliptin (ertugliflozin, −0.45% [1 mg] to −0.72% [25 mg]; sitagliptin [−0.76%]) [15]. Ertugliflozin also improved glycemic control, body weight and blood pressure in 328 patients with T2DM suboptimally controlled on metformin, and was well-tolerated [15]. Thus, ertugliflozin is an excellent candidate for therapeutic control of T2DM. However, more data are needed to clarify efficacy, duration of action, or drug–drug interactions of ertugliflozin compared to *C*-glycosides. However, glucose is not the only substrate of SGLT2; the aminoglycoside gentamicin is also transported into cells by SGLT2, and facilitates cytotoxicity *in vitro* [25]. *In vivo*, phlorizin greatly decreased gentamicin uptake by proximal tubule cells in wild-type mice, but not in *Sglt2*$^{-/-}$ mice, showing that, at least acutely, phlorizin had minimal nonspecific effects (e.g., blocking GLUTs or SGLT1) in *Sglt2*$^{-/-}$ mice [25]. SGLT1 is only weakly active in renal tissues [26]. Furthermore, co-administration of aminoglycoside-treated wild-type mice with phlorizin significantly increased serum levels of the ototoxic drug, and may potentially accelerate onset of ototoxicity [25]. These observations are similar to the more severe ototoxic and systemic side effects observed during co-administration of metformin (used as antioxidant) and gentamicin *in vivo*, in preclinical models [27]. The short-term use of ertugliflozin may have unanticipated effects (e.g., with aminoglycosides), and there may be other unexpected interactions or outcomes with long-term use of ertugliflozin. Thus, a more detailed and extended analysis of long-term ertugliflozin use is needed in a larger number of clinical subjects to support its potential clinical utility, as there are likely several specific contraindications for prescribing ertugliflozin safely. As SGLT2 also plays a role in gentamicin trafficking, a study of its combined dosing of gentamicin with ertugliflozin is warranted.

Separately, the SGLT2 functional assays as described in the patent are limited in detail. Thus, it will be hard to confirm these data without extensive pre-existing knowledge of the assays or the literature. For example, dimethyl sulfoxide (DMSO) concentrations in these assay descriptions appear to be 0.5%, levels known to induce cytotoxicity; *in vitro* concentrations of DMSO in media should not exceed 0.1% [12]. Second, the SGLT2 functional assay in the patent did not appear to use dose ranges of phlorizin as a positive control. Thus, greater clarification of experimental procedures will be welcome.

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