Glucokinase activators for type 2 diabetes
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Title Page

Title: “Glucokinase activators for type 2 diabetes: Challenges and Future Developments”

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Increased hepatic glucose output, the primary liver dysregulation associated with Type 2 diabetes mellitus (T2DM) is not directly or effectively targeted by the currently available classes of glucose-lowering medications except metformin. This unmet need might be addressed through activation of a specific enzyme-member of the hexokinase family, namely glucokinase (GK). GK serves as a “glucose-sensor” or “glucose receptor” in pancreatic cells, eliciting glucose-stimulated insulin secretion, and as glucose “gate-keeper” in hepatocytes, promoting hepatic glucose uptake and glycogen synthesis and storage. GK activation by small molecules present an alternative approach to restore/improve glycaemic control in patients with T2DM. GKAs increase insulin secretion and glycogen synthesis and hence reduce hepatic glucose output. Despite several setbacks in their development, interest in the GKA class has been renewed particularly since the introduction of a novel, dual-acting full GKA, dorzagliatin. In this article we provide an overview of the role, efficacy, safety and future developments of GK activators (GKA) in the management of T2DM.
1. Background

Type 2 diabetes mellitus (T2DM) is a complex, multifactorial disease that challenges patients, clinicians and health-care systems [1]. A combination of genetic and environmental factors results in chronic hyperglycaemia as well as a cascade of inflammatory and oxidative processes, leading to vascular complications, which are the primary cause of morbidity and mortality in T2DM. The evolving understanding of the complex multifactorial pathogenesis of T2DM [2] challenge the previously established, “simplistic” notion of a disease characterised by insulin deficiency and resistance and shift the focus onto the islet cells (β, α-cells and others) and their interplay with gut, brain, kidney and the liver [3].

When considering the increasing prevalence of T2DM globally, its progressive natural history and the still large proportion of patients not achieving optimal glycaemic control [4], the need for novel treatment strategies and targets [5] becomes even more imperative. This has resulted in the introduction of new therapies which target several of the more recently researched pathogenetic pathways associated with the gut, brain and kidney. These include glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose co-transporter-2 (SGLT2) inhibitors [6, 7].

Nevertheless, increased hepatic glucose output, the primary liver dysregulation associated with T2DM, is not directly or effectively targeted by any of the currently available classes of glucose-lowering medications except metformin [8]. This unmet need might be addressed through activation of a specific enzyme-member of the hexokinase family, namely glucokinase (GK). In this article, we will provide an overview of the role and future developments of GK activators (GKA) in the management of T2DM.

2. Overview of GK role in glucose homeostasis

Whilst glucose homeostasis is complex, it can be simplified as resulting from the net effect of a two-hormone competition between insulin and glucagon. The latter is secreted by α islet cells
of the pancreas and secures provision of energy by maintaining euglycaemia in the fasting state. This is achieved by promoting gluconeogenesis (de novo glucose production from amino acids and fat) and glycogenolysis (glycogen breakdown and glucose release from the liver), thus increasing hepatic glucose output. Free fatty acid released from adipose tissue also provides a complementary mechanism serving a similar purpose. On the other hand, insulin, secreted by β islet cells, produces a glucose-lowering effect in the fed state by promoting glucose utilisation in the periphery (mainly skeletal muscle and adipose tissue) and hepatic glucose uptake by switching liver into a “glycogen synthesis mode”. Increased glucose (in the fed state) in parallel inhibit gluconeogenesis and glycogenolysis [9].

GK serves as a “glucose-sensor” [10] in pancreatic cells, eliciting glucose-stimulated insulin secretion, and as glucose “gate-keeper” in hepatocytes, promoting hepatic glucose uptake and glycogen synthesis and storage. When GK is activated, its preferred substrate glucose is phosphorylated (with magnesium adenosine triphosphate) to glucose-6-phosphate (G6P). Glucose-6-phosphate both activates glycogen synthase and is a substrate for glycogen synthesis [11].

GK biochemical properties and kinetics serve this dual role [12], since the low affinity for glucose (K₀.₅ of ~7-8 mmol/L) restrains GK activity when glucose is in the physiological range [13]. GK is not inhibited by G6P (its end product secretion from the β-cells) and has a sigmoidal saturation curve with glucose (non-Michaelis–Menten kinetics) showing an inflection point of 4-5 mmol/l, which is close to the threshold of insulin secretion. This ensures a graded response to fluctuations in glucose levels and, when glucose is close to the physiological threshold for glucose-stimulated insulin secretion (5mM), glucokinase activity enters a plateau phase [13].

GK in the liver is maintained as an inactive complex with an endogenous inhibitor, the glucokinase regulatory protein (GKRP) when glucose concentration is less than ~10mM/L and
this confers even lower affinity for glucose in hepatic compared to pancreatic β-cells, in practice, activated only during the postprandial state to serve its function of increasing hepatic glucose uptake (Figure 1). Thus, GKRP acts as a competitive inhibitor with respect to glucose at the hepatic cell, sequestering GK in the presence of low and dissociating from GK in the presence of raised glucose concentrations.

GK is not only expressed in pancreatic β- or hepatic cells, but also in entero-endocrine cells, neurons, pancreatic α- and δ-cells, and cells in the anterior pituitary [14]. Yet, its major role in glucose homeostasis is by eliciting insulin secretion (pancreatic β-cells- glucose phosphorylation by GK is the rate-limiting step) and promoting glucose uptake and glycogen synthesis (hepatic cells).

The net effect of the above GK-mediated pathways is blood glucose lowering in both direct (insulin-mediated) and indirect ways. Therefore, it seems plausible to hypothesize that control over GK activity might constitute a novel way of intervention on glucose homeostasis, since GK activation leads to glucose lowering and GK activity is low in patients with T2DM [15]. This hypothesis is reinforced by studies of a discrete genetic subgroup of diabetes, known as maturity-onset diabetes of the young type 2 (MODY2). People with MODY2 carry inactivating, heterozygous mutations in the glucokinase gene (present in ~1 in 1,000 of the population, but most remain undiagnosed) [16], usually manifest a benign form of (mainly fasting) hyperglycemia and with low risk of microvascular complications [17], reflecting a defective “glucose-sensing” ability [16]. However, when compound heterozygosity or homozygosity is present, a more severe form of permanent neonatal diabetes may develop [18]. On the other hand, activating mutations in the glucokinase gene do rarely occur and lead to congenital hyperinsulinemic hypoglycemia with heterogenous phenotypic manifestations [19]. The above in vivo evidence, taken together with experiments on mice and human cells [20-24] corroborating the physiologic GK role in glucose homeostasis and the feasibility of its
activation, set the scene for the therapeutic rationale behind targeting glucokinase in patients with T2DM. In these patients, the gradual decline in β-cell mass resulting in defective insulin secretion, along with increased hepatic glucose output, constitute two discrete (yet interrelated) pathophysiological derangements in T2DM that could potentially be addressed by a pharmacologic upregulation of GK activity.

3. Overview of glucokinase activators (GKAs)

Several glucokinase activators have been designed and tested [25, 26] since the introduction of the first agent of this class in 2003 [27]. They are all small molecules able to bind to an allosteric site in the enzyme, stabilizing a high-affinity conformation and thus, facilitating GK activation. Interestingly, this is the same region of the enzyme where the majority of activating mutations cluster. These small-cell GKAs can be classified according the chemical structure (carbon-, urea-, 1,2,4-Substituted aryl-, 1,3,5-Substituted aryl-centered or other) [13]. Another potential classification can refer to the site of action; hepatoselective GKAs have been developed acting with or without disrupting the GK--GKRP interaction in hepatic cells [28, 29], as opposed to systemic GKAs (such as piragliatin or dorzagliatin). Additionally, full GKAs are distinguished from partial GKAs (such as agent PF-04937319). As expected, only a small minority of GKAs have reached the phase of clinical trials (detailed below and summarised in Table 1).

3.1 Clinically-tested GKAs (pharmacodynamics and safety)

In a phase Ib randomized, double-blind, placebo-controlled crossover trial in 15 individuals with mild T2DM, the GKA piragliatin (RO4389620) (25mg or 100mg) was found to cause a dose-dependent reduction of glucose levels in both fasting and fed states, mainly mediated through a generalized enhancement of β-cell function [30]. In a similar, short-
duration (8 day), dose-escalating (up to 200mg) study in 59 patients with T2DM, it was reported that piraglauatin showed rapid, dose-dependent g reduction of fasting and postprandial plasma glucose [31].

In a double-blind study the GKA MK-0941 (at doses 10, 20, 30, or 40 mg t.i.d) efficacy and safety was explored in 587 patients with T2DM treated with insulin glargine (mean baseline glycated haemoglobin (HbA1c) of 9%). By week 14, a significant 0.8% drop in HbA1c was noted, along with a significant decrease in the 2-hour post meal glucose (approximately ~40mg or 2.2 mmol/L), yet, by 30 weeks, these responses were not sustained [32]. MK-0941 was also associated with significant increases in the incidence of hypoglycaemia, hypertriglyceridemia (up to ~20% increase from baseline) and hypertension.

In a dose-ranging, placebo-controlled study in 458 patients with T2DM, the efficacy and safety of GKA AZD1656 was explored as an add-on to metformin. At four months, HbA1c showed a significant reduction, comparable to that associated with glipizide, although the glucose-lowering effect diminished over the two-month extension period, along with an increase in triglycerides [33]. The loss of efficacy, observed after the initial glucose-lowering evidence of efficacy, was replicated in a dose-ranging study in 224 Japanese patients with T2DM [34], in which no major safety concerns were noted.

The safety and efficacy of GKA PF-04937319, a systemic partial activator of glucokinase, as add-on therapy to metformin was explored in dose-ranging RCT trials involving a total of 639 adults with T2DM [35], showing equipotency with sitagliptin in glucose lowering efficacy at 3 months, when administered as a single-dose of 100mg. Split-dose regimens explored in a subsequent two-week study showed promising results with regards to safety and tolerability [36].

The GKA AMG 151 (ARRY-403) was evaluated in a multi-dosing, randomized, placebo-controlled, four-weeks phase IIa study involving 236 patients with T2DM on
metformin. AMG 151 was found to significantly reduce fasting plasma glucose when administered twice daily, but with increased incidence of hypoglycemia and hypertriglyceridemia [37].

More recently, a fourth generation GKA, dorzagliatin (Sinogliatin, HMS5552), a novel, dual-acting, allosteric systemic GKA was initially developed on the basis of piragliatin and finally evaluated in a three-month, phase 2, dose-ranging, randomised, double-blind, placebo-controlled study involving 258 Chinese patients with T2DM [38]. At week 12, a significant reduction in HbA1c was noted in patients on dorzagliatin, -0.8% with 50mg bid and ~1.1% with 75mg bid, compared to placebo. Dorzagliatin treatment primarily affected the 2-hour postprandial glucose which fell significantly in contrast to fasting glucose levels. The glucose-lowering effect was even more pronounced in the drug-naïve patients, which was interpreted as evidence supporting early use of this agent. Notably, no reports of drug-related serious adverse events or severe hypoglycaemia were recorded. In a four-week clinical study in 24 patients with T2DM, dorzagliatin was shown to also improve β-cell function, as assessed by steady and dynamic state parameters [39]. Active research on dorzagliatin is currently ongoing (NCT03173391 and NCT03141073) and long-term durability of efficacy remains to be proven. In addition, the exact mechanisms for the difference in safety profile of Dorzagliatin compared to previously GKAs remain to be investigated [40].

Encouraging results have been reported with another novel hepatoselective molecule, TTP399. A salient difference in the development of this agent was the potential compound screening procedure, which required activity in hepatic cell (glycogen and lactate production) and absence of activity in pancreatic cells (stimulation of insulin secretion) in the presence of high glucose concentrations (15mM). The molecule was shown to bind directly to GK in the same manner as glucose and express its glucose-lowering activity without affecting GK translocation [29]. The phase 2b, six-month RCT (AGATA trial), explored the efficacy and
safety of TTP339 administration (at doses of 400 and 800mg) in comparison to active drug (sitagliptin) and placebo in 190 patients with T2DM on stable dose of metformin [41]. The main finding was the -0.9% (-1.5 to -0.3) placebo-subtracted decrease in HbA1c for the 800mg dose at six months, a decrease that started to be notable only after 3 months of treatment. Of note, this significant yet relatively late onset of effect, noted in AGATA trial, was different from that observed in a preceding clinical trial (phase Ib/Iia), in which the hypoglycemic effect was noted early [29]. No significant adverse events were recorded and importantly, incidence of symptomatic hypoglycaemia was very low and similar to sitagliptin (one event). Notably, treatment with TTP399 resulted in a significant increase in HDL-c, a neutral effect on triglyceride and cholesterol, and a significant weight loss among those weighting over 100kg.

Finally, several other GKAs, ADV-1002401, TMG-123 and LY2608204 (globagliatin), have entered the clinical trial stage, yet published results are still lacking.

3.2 Challenges encountered with glucokinase activators

Both efficacy and safety issues raised important concerns with the use of older generation GKAs. Amongst them, the risk of hypoglycaemia, fatty liver induction, dyslipidaemia, and diminishing long term efficacy appear to be the most significant.

In fact, the occurrence of hypoglycaemia and dyslipidaemia, resulting from over-stimulating pancreatic and hepatic GK respectively were perceived as potential risks from the early phases of GKAs development [42, 12]. Acute, (disproportionate to the stimulus) insulin release, resulting from an exaggerated response to glucose could naturally occur as a consequence of GK activation and was always a plausible risk. The occurrence of hypoglycaemic episodes was particularly noted with piragliatin and MK-0941. To address this risk, partial activators that maintained a greater degree of dependency on glucose levels to minimize the risk of activation at low glucose concentrations [25] were developed. Hepatoselective agents were also designed and tested. The risk of hypoglycaemic events was
lower with the partial GKA PF-04937319 [35]. With regards to the pathophysiological processes associated with GK activation that may lead to dyslipidaemia, it is postulated that excessive G6-P accumulation, resulting from hepatic GK overstimulation, activates glycolysis, through the mediation of fructose 2,6-bisphosphate, which show a parallel to G6-P increase and act via feedforward allosteric activation mechanisms. This effect (activation of glycolysis) finally lead to the accumulation of acetyl-CoA (converted from pyruvate), which finally leads to an increase influx to fatty acids (via malonyl-CoA) and triglycerides or increased hepatic de-novo lipogenesis [12]. This is consistent with the reported first stage for non-alcoholic fatty liver disease (NAFLD), which can range from simple steatosis to steatohepatitis [43]. While the latter may require chronic exposure to develop, the relatively acute effect of hypertriglyceridemia was especially noted with MK-0941. Whereas the increase in triglyceride levels (<20%) may not be considered as pronounced, especially when compared to the one induced by a high-carbohydrate low-fat diet [12], it stills remains unwanted in patients with type 2 diabetes who are already prone to develop dyslipidaemia, hypertension and NAFLD [40].

Interestingly, the initial, promising glucose-lowering efficacy, noted early in the first few weeks with the introduction of a GKA, was not sustained over the course of the clinical studies. Instead, this brief window of efficacy was followed by a rapid decline of efficacy during chronic exposure to the GKA agent. This was observed with both MK-0941 and AZD1656 after approximately four months. The duration of clinical studies with GKA PF-04937319 and AMG 151 did not exceed three and one month respectively. The reasons behind this secondary failure are poorly understood. The study population administered MK-0941 possibly had no minimum critical β-cell mass left (this being necessary for GKA to act), since they had long-standing diabetes and were already on insulin treatment). This was not the case for AZD1656. It has been suggested that hepatic de novo lipogenesis or plasma hyperlipidemia
could be a direct cause for GKA failure, but this hypothesis is not universally accepted [12].

The above pattern of initial response followed by rapid decline of efficacy may contrast to the one noted in the case of hepatoselective TTP399, the glucose-lowering efficacy of which is manifested only after 3 months of treatment in AGATA trial (but not in the earlier phase trials).

Toxicity of GKAs on β-cells has also been hypothesized on the basis of histological reports in mouse models showing double-strand breaks in the deoxyribonucleic acid, likely accounting for activation of the p53 tumor suppressor and resulting β-cell death, following genetic activation of β-cell glucokinase [44, 13]. In fact, this activation resulted in a rapid decrease in blood glucose, which was not sustained, analogous to the observed trajectory in human clinical studies. Another hypothesis, proposed by Agius [12], focuses on the alleged two opposing effects of GKA on hepatic GK. The first stage is already described and occurs early when GK-induced insulin secretion corrects any abnormality in insulin/glucagon ratio and promotes GK/GKRP dissociation and hepatic GK activation. The second effect eventually sets in, when G6P and down-stream phosphate-ester intermediates of glucose metabolism accumulate to an extent that repress GK gene [45], offsetting any initial stimulatory effect induced by GKA [46], rendering their effect clinically unimportant, thus practically neutralising them. Whatever the cause for GKA diminishing efficacy over time this, in practice, may inhibit development, maturation and approval of future GKA agents.

3.3 Future developments

The minimum requirements for a novel GKA to be considered as a serious alternative to previous GKA agents include clinically relevant and sustained glycaemic efficacy, and low risk of adverse events particularly hypoglycemia, hepatic steatosis and hypertriglyceridemia. The ideal characteristics for a novel compound would be to address the long-term complications of chronic hyperglycaemia and/or modify the natural course of the disease.
Dual-acting full GKA, dorzagliatin and hepatoselective GKA, TTP399 appear to fulfil some of the first set of requirements.

In specific, Scheen provided an indirect comparison of dorzagliatin efficacy with older GKAs[40]. On the basis of HbA1c reduction, dorzagliatin appears to be superior to piragliatin, AZD1656 and PF-04937319 [40]. The placebo-adjusted ~ -0.8 % decrease in HbA1c with 75mg dorzagliatin bid was similar to that of MK-0941, although development of the latter was halted, due to safety concerns. The glucose lowering efficacy of AMG151 cannot be compared, since it has been evaluated only over the brief period of a month [37]. Importantly, dorzagliatin-induced reduction in HbA1c, already statistically significant after a month, became progressively more pronounced over the course of the study (both at two and three months), suggesting a sustained effect that might not have reached its maximum by the prespecified study end [40]. This finding is in contrast with the transient glucose-lowering effects reported with older GKAs and suggests that this may be less of an issue with this newer agent. Similarly, TTP399 has shown to be associated with a ~0.9% placebo-adjusted decrease in HbA1c and a glucose-lowering effect that extends (at least) up to six-months. These glucose-lowering effects of dorzagliatin (~0.8% decrease in HbA1c) and TTP399 (~0.9% decrease in HbA1c) may be modest, yet clinically significant, in the similar range with other glucose-lowering medications and adequate for achieving optimal glycaemic control in those patients requiring treatment intensification.

A better safety profile compared with studies of other agents from the class was also noted from the point of view of hypoglycaemia for dorzagliatin, together with no significant change in triglyceride and transaminase levels during the three-month treatment period (one case of eyelid oedema was recorded). With regards to TTP399, treatment also appears to be well tolerated with no symptomatic hypoglycaemia. Moreover, the effect of TTP399 on lipid metabolism appears to be rather favourable, with a modest but significant increase in HDL-c,
contrasting with the effects noted in studies of other agents. Importantly, it should also be noted, along with reports from studies of some of the other GKAs, that dorzagliatin is weight neutral and TTP399 may as well induce weight loss (at least in a subset of patients, with an largely unknown mechanism that remains to be elucidated).

Unfortunately, data extending beyond this three-month period for dorzagliatin and six-month period for TTP399 are lacking, so that long-term efficacy and safety are still unknown. Also unknown is the long-term net effect on microvascular complications and cardiorenal health. Considering evidence suggesting that common gene variants in GKRP may have a potentially detrimental effect on cardiorenal health, these long-term outcomes are eagerly awaited [47]. Attempting to describe the potential role of GKAs in the therapeutic algorithm in any detail would be premature, especially considering the importance of cardiovascular disease, heart failure and chronic kidney disease in selecting the optimal anti-diabetes agent(s) [48] and the lack of such data with these drugs. Nevertheless, it is reasonable to speculate that GKA are better suited as an early addition to therapy, since their action requires a minimum β-cell mass and they mainly address postprandial hyperglycemia. Whether this latter property is sufficient for GKAs to displace established second or third-line agents is unlikely unless their novelty of action confers some, as yet, unproven advantage. The reduction in fasting glucagon noted in patients receiving TTP399 may be a potential one. In addition, there may be specific patients (as yet undefined) for whom this type of therapy might be particularly beneficial as part of an individualized approach to management. Clearly much more work needs to be done in this area, including long-term demonstration of safety. This will require clinical trials with longer follow-up, adequate power and carefully selected comparators and outcomes.

4. Conclusions
GK activation by small molecules present an alternative approach to restore/improve glycaemic control in patients with T2DM. GKAs increase insulin secretion and glycogen synthesis and hence reduce hepatic glucose output. Despite several setbacks in their development, interest in the GKA class has been renewed particularly since the introduction of a novel, dual-acting full GKA, dorzagliatin and a novel hepatoselective GKA, TTP399. This is a reflection of overcoming issues of diminishing efficacy and metabolic complications with this class, problems which hindered the development of previous GKAs.
References


Table 1. Synopsis of the major clinical trials involving glucokinase activators.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Study</th>
<th>Total study N</th>
<th>Dose (mg)</th>
<th>Duration (weeks)</th>
<th>Background therapy/comparator</th>
<th>Primary effect – notable findings</th>
<th>Major safety issues and other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO4389620 (piragliatin)</td>
<td>Bonadonna et al [30]</td>
<td>15</td>
<td>25, 100</td>
<td>10-hour</td>
<td>none</td>
<td>Acute reduction of FPG PPG</td>
<td>None</td>
</tr>
<tr>
<td>RO4389620 (piragliatin)</td>
<td>Zhi et al [31]</td>
<td>59</td>
<td>10-200*</td>
<td>1</td>
<td>None</td>
<td>Acute reduction of FPG PPG</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>MK-0941</td>
<td>Meininger et al [32]</td>
<td>587 (118)*</td>
<td>10, -40 tid</td>
<td>30</td>
<td>insulin glargine ± metformin</td>
<td>HbA1c drop of −0.5 to −0.8% (not sustained, PPG)</td>
<td>hypoglycemia, hypertriglyceridemia, hypertension, loss of efficacy</td>
</tr>
<tr>
<td>AZD1656</td>
<td>Wilding et al [33]</td>
<td>458</td>
<td>20-200 bid</td>
<td>16±4</td>
<td>Add-on metformin / Glipizide</td>
<td>HbA1c drop of −0.6–1.2%, FPG</td>
<td>Increase in triglycerides</td>
</tr>
<tr>
<td>AZD1656</td>
<td>Kiyosue et al [34]</td>
<td>224</td>
<td>100 tid *</td>
<td>16</td>
<td>Drug naïve or Add-on metformin/sulfonylurea</td>
<td>Non-significant HbA1c drop of −0.2%, FPG</td>
<td>Hypoglycaemia, loss of efficacy</td>
</tr>
<tr>
<td>PF-04937319</td>
<td>Amin et al [35]</td>
<td>304</td>
<td>100 qd*</td>
<td>12</td>
<td>Add-on metformin – glimepiride</td>
<td>HbA1c drop of −0.5%, FPG</td>
<td>Hypoglycaemia,</td>
</tr>
<tr>
<td>PF-04937319</td>
<td>Amin et al [35]</td>
<td>335</td>
<td>100 qd*</td>
<td>12</td>
<td>Add-on metformin – glimepiride/ Sitagliptin</td>
<td>HbA1c drop of −0.7%, FPG</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>PF-04937319</td>
<td>Denney et al [36]</td>
<td>33</td>
<td>150+100mg</td>
<td>2</td>
<td>Add-on metformin / Sitagliptin</td>
<td>FPG</td>
<td>None</td>
</tr>
<tr>
<td>AMG 151 (ARRY-403)</td>
<td>Katz et al [37]</td>
<td>236 (54)</td>
<td>200 bid *</td>
<td>4</td>
<td>Add-on metformin</td>
<td>FPG</td>
<td>Hypoglycaemia, hypertriglyceridemia</td>
</tr>
<tr>
<td>Dorzagliatin (Sinagliatin, HMS5552)</td>
<td>Zhu et al [38]</td>
<td>258</td>
<td>50, 75 bid</td>
<td>12</td>
<td>Drug naïve or Add-on metformin</td>
<td>PPG, HbA1c drop of −0.8–1.1%</td>
<td>None</td>
</tr>
<tr>
<td>Dorzagliatin (Sinagliatin, HMS5552)</td>
<td>Zhu et al [39]</td>
<td>24</td>
<td>75 bid or qd</td>
<td>4</td>
<td>none</td>
<td>HbA1c drop of −0.8–1.0%</td>
<td>None</td>
</tr>
<tr>
<td>TTP399</td>
<td>Vella et al [41]</td>
<td>190</td>
<td>400 or 800</td>
<td>24</td>
<td>Add-on metformin / Sitagliptin</td>
<td>HbA1c drop of −0.9%</td>
<td>None</td>
</tr>
</tbody>
</table>

*multiple doses tested ^ insulin-treated, b.i.d.: bis in die, twice a day, FPG: fasting plasma glucose, PPG: post-prandial plasma glucose, tid: ter in die, three times a day, qd: quaque die, once a day