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# Dorzagliatin add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial

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**Metformin, the first-line therapy for type 2 diabetes (T2D), decreases hepatic glucose production and reduces fasting plasma glucose levels. Dorzagliatin, a dual-acting orally bioavailable glucokinase activator targeting both the pancreas and liver glucokinase, decreases postprandial glucose in patients with T2D. In this randomized, double-blind, placebo-controlled phase 3 trial, the efficacy and safety of dorzagliatin as an add-on therapy to metformin were assessed in patients with T2D who had inadequate glycemic control using metformin alone. Eligible patients with T2D ( $n = 767$ ) were randomly assigned to receive dorzagliatin or placebo (1:1 ratio) as an add-on to metformin (1,500 mg per day) for 24 weeks of double-blind treatment, followed by 28 weeks of open-label treatment with dorzagliatin for all patients. The primary efficacy endpoint was the change in glycated hemoglobin (HbA1c) levels from baseline to week 24, and safety was assessed throughout the trial. At week 24, the least-squares mean change from baseline in HbA1c (95% confidence interval (CI)) was  $-1.02\%$  ( $-1.11, -0.93$ ) in the dorzagliatin group and  $-0.36\%$  ( $-0.45, -0.26$ ) in the placebo group (estimated treatment difference,  $-0.66\%$ ; 95% CI:  $-0.79, -0.53$ ;  $P < 0.0001$ ). The incidence of adverse events was similar between groups. There were no severe hypoglycemia events or drug-related serious adverse events in the dorzagliatin and metformin combined therapy group. In patients with T2D who experienced inadequate glycemic control with metformin alone, dorzagliatin resulted in effective glycemic control with good tolerability and safety profile (NCT03141073).**

The prevalence of T2D continues to increase worldwide. In 2021, approximately 537 million (one in ten) adults (aged 20–79 years) were living with diabetes worldwide, of whom 90–95% were diagnosed with T2D<sup>1</sup>. As recommended in various guidelines<sup>2,3</sup>, metformin is the preferred first-line therapy for T2D. The anti-hyperglycemic effect of metformin primarily originates from a reduction in hepatic glucose output<sup>4</sup>. The loss of efficacy of metformin monotherapy treatment in patients with T2D is associated with continued deterioration of  $\beta$ -cell function<sup>5,6</sup>. An addition of other anti-diabetic medications to metformin is often required after a few years, and various drugs with different mechanisms of action have emerged as add-on options<sup>2</sup>. However, the ongoing decline in  $\beta$ -cell function remains an unmet need in patients with T2D, some of whom eventually progress to insulin-dependent diabetes and develop additional complications.

Glucokinase is an enzyme that acts as a glucose sensor and plays a key role in glucose homeostasis<sup>7</sup>. Glucokinase regulates glucose-stimulated insulin secretion (GSIS) and intrinsic glucagon release in the pancreas and glucagon-like peptide-1 (GLP-1) secretion in the intestine while modulating hepatic glucose uptake and glycogen synthesis in the liver<sup>8–11</sup>. Decreased glucokinase expression in patients with T2D leads to the loss of glucose sensitivity with increased blood glucose fluctuations<sup>12–14</sup>. Pharmacological activation of glucokinase by small-molecule glucokinase activators (GKAs) showed their effects on the glucose-sensing function of glucokinase through regulating the secretion of hormones such as insulin, glucagon and GLP-1 in response to glucose changes<sup>11,15–18</sup>. These results suggested that GKAs have the potential to improve glucose sensitivity and help maintain glycemic homeostasis in patients with diabetes and might represent an alternative treatment for T2D<sup>19,20</sup>.

A full list of affiliations appears at the end of the paper.

The development of GKAs to treat diabetes has experienced a long journey with many challenges. Although several GKAs have progressed into clinical studies, few have been studied beyond phase 2 due to hypoglycemia, hypertriglyceridemia, tachyphylaxis or liver-associated adverse effects<sup>21–26</sup>. Among the initially promising of several GKAs, MK-0941, a dual-acting full GKA, improved glycemic control in early studies but lost its efficacy in a time-dependent manner from 14 to 22 weeks of treatment, resulting in a high incidence of hypoglycemia when added to stable-dose insulin glargine in patients with T2D<sup>26</sup>. The primary explanation for this effect appears to be that MK-0941 allosterically activates glucokinase but also reduces the cooperativity of the enzyme for glucose, as shown by a reduction in the Hill coefficient<sup>27</sup>. This reduction in cooperativity with glucose allows some activation of glucokinase even at low glucose concentrations, leading to a substantial decrease in the threshold of GSIS. A lack of sustained glycemic control in patients with T2D is likely attributable to the continued activation of glucokinase in the face of normoglycemia<sup>26,27</sup>. Thus, it is critical that GKAs maintain the role of glucokinase as a glucose sensor by retaining glucose cooperativity and avoiding inappropriate activation of the enzyme under conditions of low plasma glucose levels.

Dorzagliatin is an orally bioavailable, dual-acting, full GKA that activates both pancreatic and hepatic glucokinase in a glucose-dependent manner. Dorzagliatin regulates the glucose-stimulated secretion of the hormones, such as the insulin in the pancreas and GLP-1 in the intestine, while optimizing the glucose and insulin signals in the liver to control hepatic glucose metabolism in patients with T2D<sup>11,15–17</sup>. A phase 2 clinical study (12-week monotherapy) demonstrated that dorzagliatin improved the glucose disposition index and reduced insulin resistance index homeostasis model assessment-IR (HOMA-IR), and these effects were maintained 1 week after drug withdrawal<sup>17</sup>. Dorzagliatin improved glycemic control when administered orally for 24 weeks at a dose of 75 mg twice daily (BID) to drug-naïve patients with T2D as monotherapy in the phase 3 SEED trial<sup>28</sup> with an improvement in  $\beta$ -cell function index homeostasis model assessment 2- $\beta$  (HOMA2- $\beta$ ) over placebo. Given that dorzagliatin acts by improving glucose sensitivity and  $\beta$ -cell function, its combination with metformin has the potential to offer synergistic benefits in the treatment of T2D. No drug–drug interactions between dorzagliatin and metformin were observed in the phase 1 clinical study in patients with T2D<sup>29</sup>. Here we report the efficacy and safety of dorzagliatin in combination with metformin in the DAWN trial, a phase 3 clinical trial in patients with T2D who were unable to achieve adequate glycemic control with metformin alone.

## Results

**Patient demographics and clinical characteristics.** Patients were recruited from 11 October 2017 to 30 August 2019, and the last patient visit was conducted on 31 August 2020. Of the 1,721 patients screened, 767 eligible patients were randomly assigned to one of the two treatment groups: 382 patients were assigned to receive dorzagliatin (75 mg BID) and metformin (1,500 mg daily), and 385 patients were assigned to receive placebo and metformin (1,500 mg daily) (Fig. 1). In total, 766 patients took at least one dose of the study drug and were included in the safety analysis set (SS); 751 patients completed at least one post-randomization measurement and were included in the full analysis set (FAS). Among patients who underwent randomization, 692 (90.2%) completed 24 weeks of double-blind treatment (349 patients (91.4%) in the dorzagliatin and metformin group and 343 patients (89.1%) in the placebo and metformin group). All patients were switched to dorzagliatin and metformin after 24 weeks. Subsequently, 646 patients (84.2%) completed 52 weeks of treatment (330 patients (86.4%) in the original dorzagliatin and metformin group and 316 patients (82.1%) in

the original placebo and metformin group) (Fig. 1 and Extended Data Fig. 1). Among the 767 randomized patients, 475 (62%) were male and 292 (38%) were female. The average age of the study patients was  $54.5 \pm 9.6$  years, and the average disease duration was  $71.5 \pm 55.8$  months. The patients had an average body mass index (BMI) of  $25.9 \pm 3.1$  kg m<sup>-2</sup> and a mean HbA1c value of  $8.3 \pm 0.6\%$  at baseline. The demographic and baseline characteristics were similar between the two groups (Table 1).

**Efficacy outcomes.** The study met the primary endpoint. HbA1c levels were reduced from baseline by 1.02% (95% CI:  $-1.11, -0.93$ ) in the dorzagliatin and metformin group at week 24, whereas the HbA1c decreased by 0.36% (95% CI:  $-0.45, -0.26$ ) in the placebo and metformin group (estimated treatment difference (ETD),  $-0.66\%$ ; 95% CI:  $-0.79, -0.53$ ;  $P < 0.0001$ ) (Fig. 2a, Table 2 and Supplementary Table 1).

The secondary endpoint of the time course of decreases in the HbA1c levels showed that reductions of HbA1c in the dorzagliatin and metformin group started at week 4 and were maintained compared to the placebo group until the end of the 24-week treatment period (Fig. 2b and Table 2). At week 24, 44.4% of the patients in the dorzagliatin and metformin group and 10.7% of the patients in the placebo and metformin group reached HbA1c levels of  $<7.0\%$  (odds ratio (OR), 7.60; 95% CI: 5.05, 11.42). Around 40.6% of patients in the dorzagliatin and metformin group achieved HbA1c levels of  $<7.0\%$  at week 8 (versus 5.6% in the placebo and metformin group) and were sustained until week 24 (Table 2).

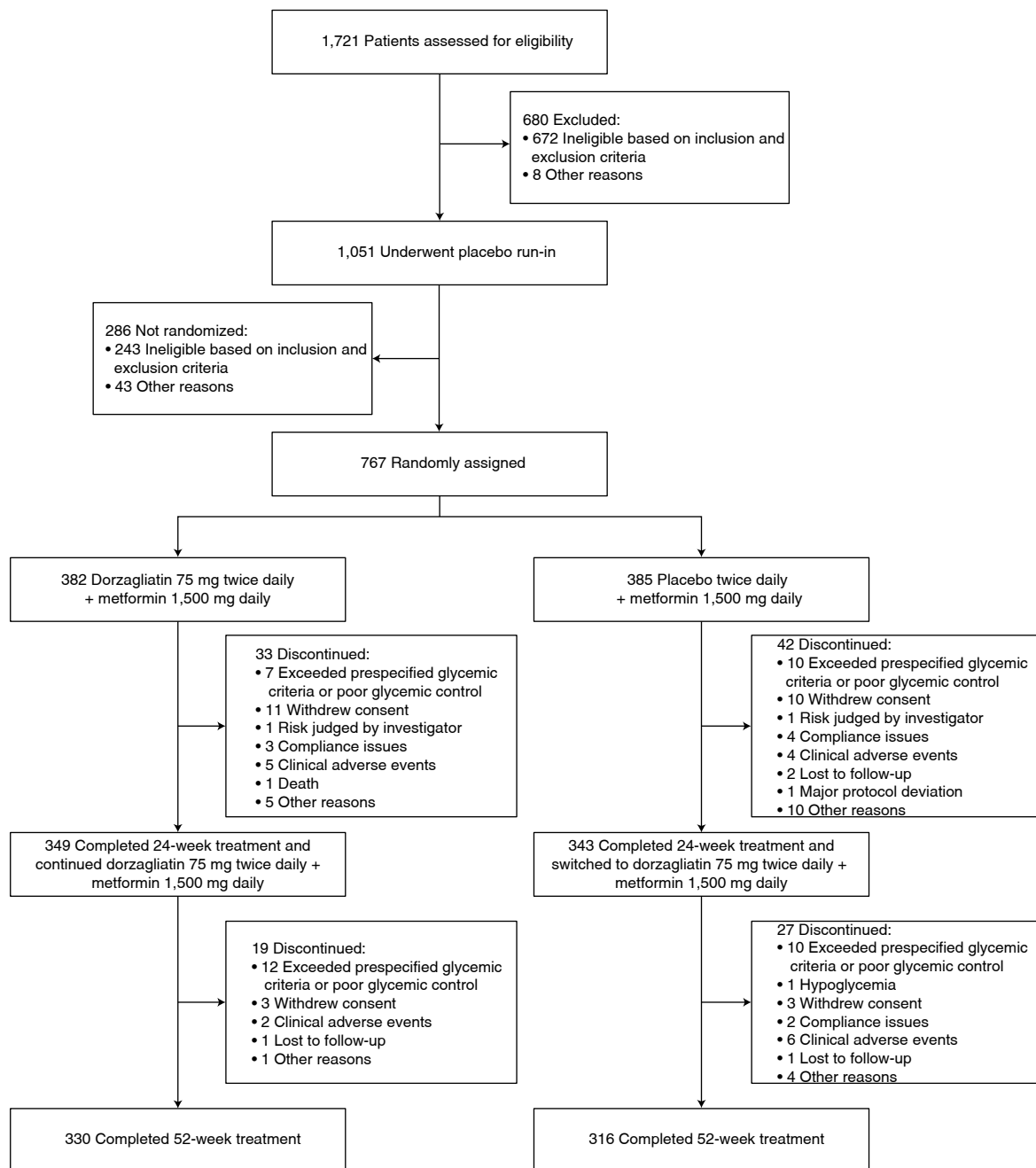
The change from baseline of fasting plasma glucose (FPG) and 2-hour post-challenge plasma glucose (2h-PPG) at week 24 were also pre-specified secondary endpoints (Fig. 2c,d, Table 2 and Supplementary Tables 2 and 3). At week 24, the reduction in the 2h-PPG level from baseline with dorzagliatin and metformin was greater than that observed for placebo and metformin (ETD,  $-44.64$  mg dl<sup>-1</sup>; 95% CI:  $-53.28, -35.82$ ) (Fig. 2c, Table 2 and Supplementary Table 3). The FPG levels in the dorzagliatin and metformin group were also reduced further than those in the placebo and metformin group at week 24 (ETD,  $-6.84$  mg dl<sup>-1</sup>; 95% CI:  $-12.06, -1.62$ ) (Fig. 2d, Table 2 and Supplementary Table 2).

Exploratory endpoints of improvements in HOMA2- $\beta$  and reduction of HOMA2-IR from baseline to week 24 in the dorzagliatin and metformin group were greater than those in the placebo and metformin group (ETD for HOMA2- $\beta$ , 2.43; 95% CI: 0.59, 4.26 and ETD for HOMA2-IR,  $-0.08$ ; 95% CI:  $-0.15, -0.01$ ) (Table 2).

The reduced HbA1c levels in the dorzagliatin and metformin group were sustained from week 24 to week 52 in the open-label extension arm of the study (Fig. 2e). A similar decrease in HbA1c levels was observed when the placebo and metformin group was crossed over to dorzagliatin and metformin treatment during the open-label extension; HbA1c levels were reduced over the first 4–8 weeks after the crossover and sustained out to week 52 (Fig. 2e and Supplementary Table 4).

Post hoc analyses were performed to explore outcomes other than primary and secondary outcomes. The composite endpoint (HbA1c level of  $<7.0\%$  without hypoglycemia and no weight gain) was achieved by 26.6% of patients in the dorzagliatin and metformin group, whereas that in the placebo and metformin group was 7.7% at week 24 (OR, 4.31; 95% CI: 2.75, 6.75) (Table 2).

**Safety outcomes.** During the 24-week double-blind treatment period, at least one adverse event (AE) was reported in 299 of the 382 patients (78%) in the dorzagliatin and metformin group and in 278 of the 384 patients (72%) in the placebo and metformin group (Table 3). Most AEs were mild and resolved while on treatment, and the investigators considered these AEs unrelated to drug administration (Supplementary Table 7). No clustering of serious adverse events (SAEs) was observed in any organ system (Supplementary



**Fig. 1 | DAWN study patient disposition.** DAWN study patient disposition flow diagram for the entire trial. Note that ten patients did not meet the inclusion and exclusion criteria but were included in the run-in period. In total, 767 patients were randomized, and 766 patients who took at least one dose of the study drug were included in the SS. The FAS included 751 patients who took at least one dose of the study drug and had at least one post-treatment measurement of the primary endpoint during the double-blind treatment period. Two patients did not meet the criteria for randomization but were randomized, one of whom was included in the FAS and the other was not, as this patient did not take at least one dose of the study drug.

Table 8). No severe hypoglycemia events or drug-related SAEs were observed. The AEs that occurred in at least 5% were upper respiratory tract infection, hyperlipidemia, protein present in urine, hyperuricemia and hypertriglyceridemia, in order, which were mostly not related to the investigational drug, as judged by investigators (Table 3). No significant differences in the type and severity of AEs were observed between the two groups (Table 3). The incidence of drug-related AEs, as assessed by the investigators, was low. During the open-label treatment period, the type and incidence rate of both AEs and SAEs remained the same as those that occurred during the double-blind treatment period (Supplementary Table 7).

Clinically meaningful hypoglycemia (that is, blood glucose level  $<54 \text{ mg dl}^{-1}$ ) was reported in three (0.8%) of the 382 patients in the dorzagliatin and metformin group during the 24-week double-blind period and in one (0.1%) of the 692 patients during the open-label treatment period (Supplementary Table 7), whereas zero was reported in the placebo and metformin group during either the 24-week double-blind or the open-label treatment period (Table 3 and Supplementary Table 7).

During the double-blind treatment period, BMI decreased, and no significant differences were observed between the two groups. No significant differences in blood pressure were observed between

**Table 1 | Baseline characteristics of the patients**

Characteristic	Dorzagliatin and metformin (n = 382)	Placebo and metformin (n = 385)	Total (n = 767)
Age, years	54.6 ± 10.0	54.4 ± 9.2	54.5 ± 9.6
Sex, n (%)			
Female	137 (36)	155 (40)	292 (38)
Male	245 (64)	230 (60)	475 (62)
Duration of diabetes, months	73.7 ± 58.5	69.4 ± 53.0	71.5 ± 55.8
Body weight, kg	70.8 ± 11.4	71.5 ± 12.2	71.1 ± 11.8
Body mass index <sup>a</sup> , kg m <sup>-2</sup>	25.7 ± 3.0	26.1 ± 3.2	25.9 ± 3.1
Blood pressure, mmHg			
Systolic	125.7 ± 12.5	125.3 ± 12.3	125.5 ± 12.4
Diastolic	79.9 ± 8.0	80.3 ± 8.1	80.1 ± 8.1
HbA1c, %	8.3 ± 0.6	8.3 ± 0.6	8.3 ± 0.6
FPG, mg dl <sup>-1</sup>	175.9 ± 28.9	179.1 ± 30.0	177.5 ± 29.5
2h-PPG, mg dl <sup>-1</sup>	338.8 ± 55.0	343.4 ± 54.0	341.1 ± 54.6
Fasting C-peptide <sup>b</sup> , ng ml <sup>-1</sup>	1.52 ± 0.55	1.61 ± 0.65	1.56 ± 0.60
HOMA2-β <sup>b</sup>	31.11 ± 11.82	31.43 ± 12.65	31.27 ± 12.24
HOMA2-IR <sup>b</sup>	1.39 ± 0.52	1.49 ± 0.70	1.44 ± 0.62
ALT <sup>c</sup> , U L <sup>-1</sup>	23.0 ± 13.7	24.3 ± 13.9	23.7 ± 13.8
AST <sup>c</sup> , U L <sup>-1</sup>	19.8 ± 8.6	21.0 ± 9.2	20.4 ± 8.9
TBil <sup>c</sup> , μmol L <sup>-1</sup>	10.9 ± 4.9	11.0 ± 4.8	11.0 ± 4.9
TG <sup>c</sup> , mmol L <sup>-1</sup>	1.88 ± 1.30	1.90 ± 1.13	1.89 ± 1.22
TC <sup>c</sup> , mmol L <sup>-1</sup>	4.51 ± 0.89	4.54 ± 0.86	4.53 ± 0.88
LDL-C <sup>c</sup> , mmol L <sup>-1</sup>	2.47 ± 0.78	2.47 ± 0.74	2.47 ± 0.76
HDL-C <sup>c</sup> , mmol L <sup>-1</sup>	1.22 ± 0.28	1.23 ± 0.28	1.22 ± 0.28
Creatinine, μmol L <sup>-1</sup>	67.6 ± 12.92	67.5 ± 13.32	67.5 ± 13.11
Urea nitrogen, mmol L <sup>-1</sup>	5.31 ± 1.316	5.17 ± 1.300	5.24 ± 1.309
Serum uric acid, μmol L <sup>-1</sup>	314.0 ± 69.74	320.5 ± 78.58	317.3 ± 74.33
eGFR <sup>c</sup> , ml/min/1.73 m <sup>-2</sup>	99.6 ± 19.3	98.2 ± 19.0	98.9 ± 19.2

The values are reported as the means ± s.d. Plasma glucose levels were converted to millimoles per liter by dividing the value by 18. <sup>a</sup>BMI is calculated as weight in kilograms divided by the square of height in meters. <sup>b</sup>Fasting C-peptide levels, HOMA2-β and HOMA2-IR were calculated in 751 patients included in the FAS. <sup>c</sup>ALT, AST, TBil, TG, TC, LDL-C, HDL-C, creatinine, urea nitrogen, serum uric acid levels and eGFR were calculated in 766 patients included in the SS population.

the two groups. All laboratory indicators related to liver and kidney function were within the normal range during the study. Regarding blood lipid levels, the total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were within the normal range during the study, and triglyceride (TG) levels showed slight increases at week 24 without further changes over the 52 weeks of treatment (Table 4). The incidence of hyperlipidemia AEs was 14% in the dorzagliatin and metformin group and 9% in the placebo and metformin group. Only two cases in the dorzagliatin and metformin group and one case in the placebo and metformin group of hyperlipidemia AEs were judged by investigators to be related to the investigational product (Table 3).

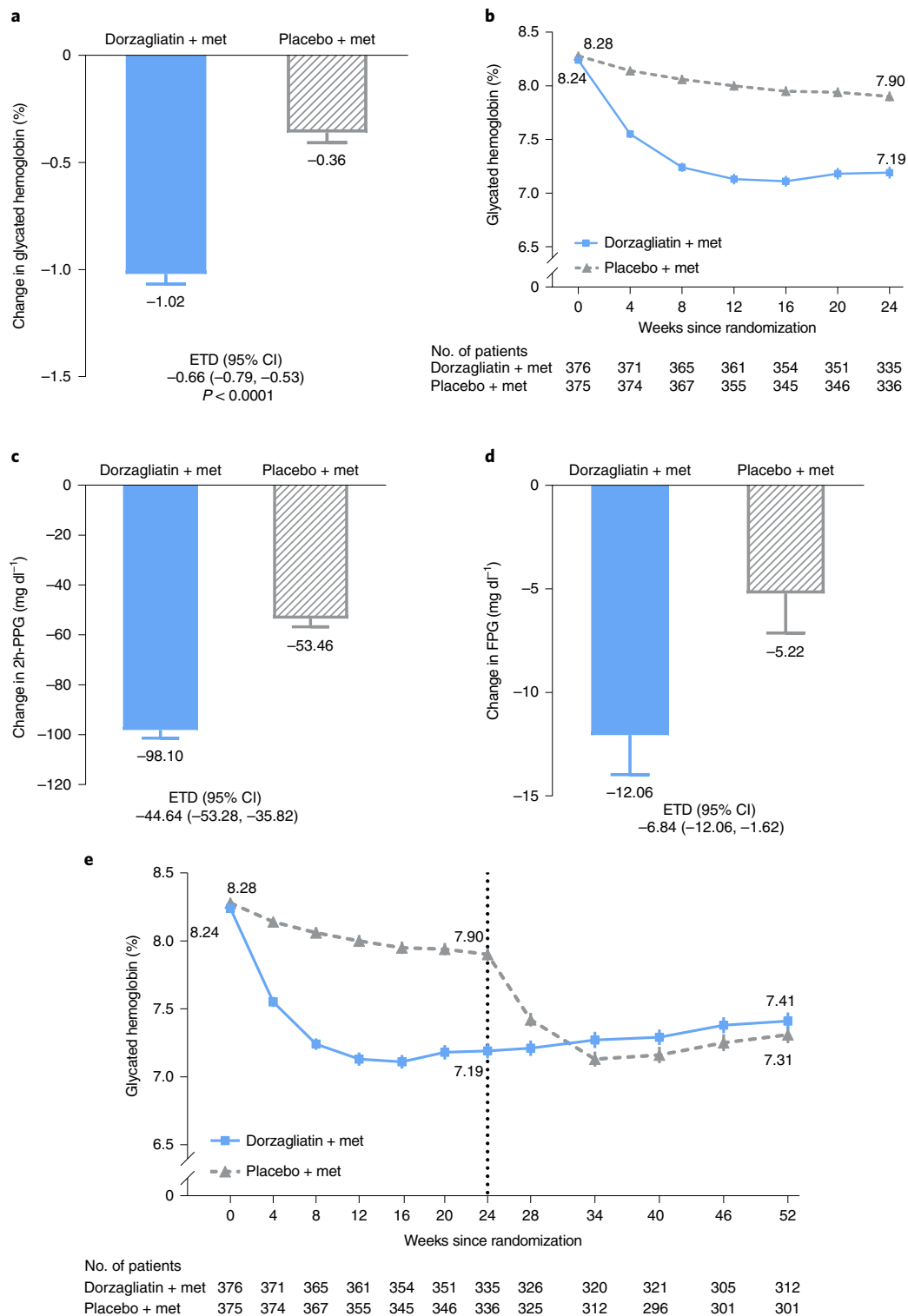
## Discussion

This randomized, placebo-controlled phase 3 study evaluated the 24-week efficacy and the 52-week safety of dorzagliatin, a dual-acting full allosteric GKA, in combination with metformin in patients with T2D who had inadequate glycemic control with metformin alone. The DAWN study achieved its primary efficacy endpoint of reduction in HbA1c levels at 24 weeks, with a significant placebo-adjusted reduction in HbA1c of 0.66% when dorzagliatin was added to 1,500 mg of daily metformin. Dorzagliatin as an add-on therapy to metformin had a good tolerability and safety profile during the entire 52-week treatment period, with no excess occurrence of drug-related SAEs or severe hypoglycemia in the dorzagliatin and metformin group.

The participants enrolled in the DAWN trial represented patients with T2D with a mean disease duration of approximately 6 years who have a baseline HbA1c level of approximately 8.3% and a relatively high 2h-PPG level of approximately 340 mg dl<sup>-1</sup> (Table 1) with a relatively low BMI of 26 kg m<sup>-2</sup> compared to patients with diabetes from the United States<sup>30</sup>. The substantially high level of post-challenge glucose in these patients likely resulted from impaired GSIS and decreased glucokinase expression in both the pancreas and liver, which may have led to reduced hepatic glucose uptake and increased hepatic glucose production<sup>12,13</sup>. Significant reduction in 2h-PPG was observed when dorzagliatin was used as an add-on to metformin, which was in line with a significant improvement in both the β-cell function and insulin resistance, as measured by HOMA2-β and HOMA2-IR. The fast onset of HbA1c reduction was similar to that observed in the SEED study<sup>28</sup>, suggesting that dorzagliatin addresses the common defects in patients with diabetes at the different stages of the disease. Further studies to evaluate the mechanism of action of dorzagliatin in the modulation of gluconeogenesis, glycogenolysis and the glucokinase activity on endogenous glucose production in T2D are ongoing (NCT05098470).

Several GKAs have been tested in clinical studies in combination with metformin. PF-04937319, a dual-acting partial allosteric GKA, was studied as an add-on therapy to metformin compared to glimepiride and sitagliptin in adults with T2D<sup>24</sup>. PF-04937319 showed a similar placebo-adjusted reduction in HbA1c as sitagliptin (0.46% versus 0.43%) with a similar incidence of hypoglycemia (5.1% versus 1.8%) after 12-month treatment. This partial GKA has shown no effect on the reduction of FPG. Glimepiride as an add-on to metformin resulted in a higher placebo-adjusted HbA1c reduction of 0.83% but a much higher incidence of hypoglycemia of 34.4% in the same study. PF-04937319 showed good safety and tolerability profile in this 12-week study with no clinically significant changes in lipids, liver enzyme levels and blood pressure profile, which is different from what has been reported in a phase 2 study of MK-0941 as an add-on to insulin in patients with T2D. PF-04937319 produces human metabolite with N-demethylation and is currently under phase 3 evaluation in patients with T2D with an alternative dose regimen<sup>31,32</sup>.

Our study does have limitations, which should be considered when interpreting the results. The foremost limitation was that it was designed for registration in China and was conducted in only one country. Additionally, the DAWN study was designed to evaluate the efficacy and safety of dorzagliatin as an add-on to metformin in patients who failed to achieve optimal glycemic control with a full dose of metformin at 1,500 mg daily. Therefore, results from the population selected by the inclusion and exclusion criteria, including medication history and ranges of HbA1c levels, C-peptide levels and hepatic and renal parameters in this study, might not be generalizable to broader patient populations. A second limitation is that this study was designed as an add-on to metformin standard of care therapy and did not compare the effects of dorzagliatin with other anti-diabetic drugs. The efficacy and safety outcomes of combination treatments involving dorzagliatin with multiple anti-diabetic



**Fig. 2 | Primary and secondary efficacy endpoints.** **a**, The primary endpoint: LS mean changes in the HbA1c level from baseline to week 24 in patients who received either dorzagliatin and metformin or placebo and metformin. The ETD and corresponding 95% CI were estimated using, in the FAS, an MMRM without missing value imputation (dorzagliatin,  $n = 374$ ; placebo,  $n = 374$ ) ( $P < 0.0001$ ). **b**, The mean HbA1c level recorded at each visit over 24 weeks in patients who received either dorzagliatin and metformin or placebo and metformin. **c**, The LS mean change in 2h-PPG levels from baseline. ETD and 95% CI were estimated in the FAS using an MMRM (dorzagliatin,  $n = 360$ ; placebo,  $n = 355$ ). **d**, The LS mean change in FPG from baseline. ETD and 95% CI were estimated in the FAS using an MMRM (dorzagliatin,  $n = 374$ ; placebo,  $n = 374$ ). **e**, The mean HbA1c levels measured at each visit over 52 weeks. The FAS comprised all randomized patients who took at least one dose of the study drug and had at least one post-treatment measurement of the primary endpoint during the double-blind treatment period. All statistical tests were two-sided at a significance level of 0.05, and no adjustments were made for multiplicity. Data in **a**, **c** and **d** are presented as LS mean  $\pm$  s.e.; data in **b** and **e** are presented as mean  $\pm$  s.e. Met: metformin.



**Table 2 | Changes in the efficacy endpoints from baseline to weeks 24 and 52**

Endpoints	Dorzagliatin and metformin (n = 376)	Placebo and metformin (n = 375)	ETD, dorzagliatin vs. placebo (95% CI)
HbA1c, %			
Week 4	-0.71 ± 0.02	-0.17 ± 0.02	-0.54 (-0.61, 0.48)
Week 12	-1.13 ± 0.04	-0.28 ± 0.04	-0.85 (-0.96, 0.74)
Week 24	-1.02 ± 0.05	-0.36 ± 0.05	-0.66 (-0.79, -0.53)
P value	-	-	<0.0001
Week 52 <sup>a</sup>	-0.81 ± 1.059	-0.96 ± 0.971	-
2h-PPG, mg dl <sup>-1</sup>			
Week 12	-99.5 ± 3.1	-45.0 ± 3.1	-54.5 (-62.82, -46.44)
Week 24	-98.1 ± 3.3	-53.5 ± 3.3	-44.6 (-53.28, -35.82)
Week 52 <sup>a</sup>	-92.2 ± 69.8	-104.9 ± 72.5	-
FPG, mg dl <sup>-1</sup>			
Week 4	-16.9 ± 1.5	-0.9 ± 1.5	-16.0 (-19.98, -11.88)
Week 12	-15.7 ± 1.6	-4.5 ± 1.6	-11.0 (-15.30, -6.84)
Week 24	-12.1 ± 1.9	-5.2 ± 1.9	-6.8 (-12.06, -1.62)
Week 52 <sup>a</sup>	-8.6 ± 37.4	-15.3 ± 35.8	-
HbA1c <7.0% <sup>b</sup> , %			
Week 8	40.6	5.6	-
Week 24	44.4	10.7	7.60 (5.05, 11.42)
Composite endpoint <sup>b</sup> (HbA1c <7.0% without hypoglycemia and no weight gain), %			
Week 24	26.6	7.7	4.31 (2.75, 6.75)
Fasting insulin, μU ml <sup>-1</sup>			
Week 24	-0.59 ± 2.76	3.51 ± 2.756	-4.10 (-11.76, 3.56)
HOMA2-β <sup>c</sup>			
Week 24	3.82 ± 0.71	1.40 ± 0.70	2.43 (0.59, 4.26)
HOMA2-IR <sup>c</sup>			
Week 24	-0.17 ± 0.03	-0.09 ± 0.03	-0.08 (-0.15, -0.01)

The values are presented as the estimated LS mean changes ± s.e. from baseline. The LS mean differences and corresponding 95% CIs were estimated in the FAS using an MMRM. <sup>a</sup>Values are presented as arithmetic means ± s.d. and were calculated using paired t-tests for baseline comparisons. <sup>b</sup>The response rate was estimated in the FAS with the data imputed by LOCF. ETD is presented as the OR and 95% CI and was calculated using logistic regression analysis. <sup>c</sup>The values are presented as the estimated LS means ± s.e. The LS mean differences in the FAS were calculated using ANCOVA with the data imputed by the LOCF. Data were computed using the HOMA2 Calculator version 2.2.3: <https://www.dtu.ox.ac.uk/homacalculator/download.php>. All statistical tests were two-sided at a significance level of 0.05.

drugs need to be evaluated in future international multi-center clinical trials. Results from a clinical pharmacological evaluation indicated the benefits of dorzagliatin as an add-on to sitagliptin and empagliflozin in patients with T2D in the United States<sup>11</sup>. A significant reduction in the plasma glucose and an increase in the GSIS in the combination therapy were observed<sup>11</sup>. Third, because the study objective was to observe the efficacy at 24 weeks and safety

**Table 3 | AEs and hypoglycemic events recorded during the 24-week double-blind treatment period**

Event	Dorzagliatin and metformin (n = 382)	Placebo and metformin (n = 384)
	No. of patients (%)	No. of patients (%)
Any AEs	299 (78)	278 (72)
AEs related to dorzagliatin <sup>#</sup>	53 (14)	36 (9)
AEs leading to drug discontinuation <sup>a</sup>	1 (0.3)	3 (0.8)
AEs in ≥5% of patients <sup>b</sup>		
Upper respiratory tract infection	54 (14)	52 (14)
Related to the study drug <sup>c</sup>	0	0
Hyperlipidemia	52 (14)	33 (9)
Related to the study drug <sup>c</sup>	2 (0.5)	1 (0.3)
Protein present in urine	30 (8)	30 (8)
Related to the study drug <sup>c</sup>	0	3 (0.8)
Hyperuricemia	37 (10)	14 (4)
Related to the study drug <sup>c</sup>	3 (0.8)	0
Hypertriglyceridemia	21 (6)	11 (3)
Related to the study drug <sup>c</sup>	7 (2)	2 (0.5)
Any SAEs	19 (5)	17 (4)
SAEs leading to drug discontinuation <sup>d</sup>	3 (0.8)	4 (1.0)
SAEs related to the study drug	0	0
Any hypoglycemia		
Severe hypoglycemia <sup>e</sup>	0	0
Clinically significant hypoglycemia (blood glucose level <54 mg dl <sup>-1</sup> )	3 (0.8)	0

AEs and SAEs that occurred during the 24-week double-blind treatment period among the patients in the safety population are included in the table and presented with their preferred terms based on the *Medical Dictionary for Regulatory Activities*, version 23.0 (ref. <sup>33</sup>). The data were obtained from patients who received at least one dose of a study drug and included events that occurred during treatment or within 7 days after the last receipt of a study drug. <sup>#</sup>Possibly or very likely related to dorzagliatin, as assessed by the investigators. <sup>a</sup>SAEs that led to drug discontinuation are not included. <sup>b</sup>AEs in at least 5% of the patients in the dorzagliatin and metformin group or the placebo and metformin group are listed in the table. <sup>c</sup>AEs in at least 5% of the patients related to dorzagliatin were defined as AEs and deemed by the investigators to be very likely or probably related to dorzagliatin or placebo. <sup>d</sup>During the 24-week double-blind treatment period, one patient in the dorzagliatin and metformin group died (confirmed by the external drug safety committee as sudden death). The patient had T2D and established cardiovascular disease, and the event was considered unlikely to be related to dorzagliatin by both the investigator and the sponsor. <sup>e</sup>Severe hypoglycemia is defined as severe cognitive impairment requiring assistance from another person for recovery.

over 52 weeks, no control group was incorporated into the design of the open-label treatment period from week 24 to week 52. Thus, a prolonged and placebo-controlled study will address the question of longer-term efficacy after 24 weeks of treatment. The total observation period of 1 year was also insufficient to evaluate the long-term safety profile and benefits of dorzagliatin. Finally, we note that self-monitoring of blood glucose and self-reporting of hypoglycemia might not fully capture the incidence of hypoglycemia in this study, which might have been observed with additional clinical monitoring; therefore, it is possible that asymptomatic incidents of hypoglycemia were underreported.

In summary, DAWN showed that using dorzagliatin as an add-on to metformin can provide effective glycemic control with a good tolerability and safety profile in patients with T2D who had inadequate control with metformin alone.

**Table 4 | Changes in selected laboratory results and vital signs**

	Dorzagliatin and metformin (n = 382)		Placebo and metformin (n = 384)	
	Week 24	Week 52	Week 24	Week 52
Body weight, kg	-0.19 ± 2.27	-0.50 ± 2.02	-0.45 ± 2.16	-0.30 ± 2.22
BMI, kg m <sup>-2</sup>	-0.07 ± 0.82	-0.18 ± 0.74	-0.17 ± 0.79	-0.11 ± 0.84
Systolic blood pressure, mmHg	-0.18 ± 12.18	-0.20 ± 12.94	-1.20 ± 12.64	2.02 ± 12.52
Diastolic blood pressure, mmHg	0.16 ± 8.47	0.00 ± 9.08	-1.42 ± 7.93	-0.08 ± 8.00
TG, mmol L <sup>-1</sup>	0.41 ± 1.40	0.40 ± 1.64	0.03 ± 0.97	0.59 ± 1.83
TC, mmol L <sup>-1</sup>	0.11 ± 0.70	0.18 ± 0.77	0.01 ± 0.69	0.17 ± 0.68
LDL-C, mmol L <sup>-1</sup>	-0.09 ± 0.57	-0.03 ± 0.62	-0.01 ± 0.59	-0.02 ± 0.56
HDL-C, mmol L <sup>-1</sup>	0.01 ± 0.17	0.04 ± 0.16	0.00 ± 0.17	0.02 ± 0.17
ALT, U L <sup>-1</sup>	5.4 ± 12.2	3.7 ± 12.9	0.1 ± 15.7	5.0 ± 16.0
AST, U L <sup>-1</sup>	4.8 ± 8.5	3.8 ± 9.1	0.0 ± 8.7	5.1 ± 13.0
TBil, µmol L <sup>-1</sup>	-1.0 ± 3.8	-0.6 ± 3.9	-0.3 ± 3.5	-1.0 ± 3.4
Creatinine, µmol L <sup>-1</sup>	0.3 ± 7.13	1.9 ± 7.47	0.3 ± 7.02	1.4 ± 6.75
Urea nitrogen, mmol L <sup>-1</sup>	-0.03 ± 1.331	-0.02 ± 1.255	-0.06 ± 1.269	0.03 ± 1.240
Serum uric acid, µmol L <sup>-1</sup>	29.9 ± 69.75	26.3 ± 57.23	-4.0 ± 56.30	21.5 ± 56.42
eGFR, ml/min/1.73 m <sup>2</sup>	-0.61 ± 11.74	-2.53 ± 11.70	-0.46 ± 12.56	-2.13 ± 11.84

The values are presented as the arithmetic means ± s.d.

### Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-022-01803-5>.

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### References

- International Diabetes Federation. *IDF Diabetes Atlas* 10th edn (International Diabetes Federation, 2021).
- American Diabetes Association Professional Practice Committee et al. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. *Diabetes Care* **45**, S125–S143 (2022).
- Cosentino, F. et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur. Heart J.* **41**, 255–323 (2020).
- Rena, G., Hardie, D. G. & Pearson, E. R. The mechanisms of action of metformin. *Diabetologia* **60**, 1577–1585 (2017).
- Turner, R. C., Cull, C. A., Frighi, V. & Holman, R. R. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK prospective diabetes study (UKPDS) group. *JAMA* **281**, 2005–2012 (1999).
- Fonseca, V. A. Defining and characterizing the progression of type 2 diabetes. *Diabetes Care* **32**, S151–S156 (2009).
- Matschinsky, F. M. & Wilson, D. F. The central role of glucokinase in glucose homeostasis: a perspective 50 years after demonstrating the presence of the enzyme in islets of Langerhans. *Front. Physiol.* **10**, 148 (2019).
- Lenzen, S. A fresh view of glycolysis and glucokinase regulation: history and current status. *J. Biol. Chem.* **289**, 12189–12194 (2014).
- Matschinsky, F. M. Regulation of pancreatic β-cell glucokinase: from basics to therapeutics. *Diabetes* **51**, S394–S404 (2002).
- Agius, L. Glucokinase and molecular aspects of liver glycogen metabolism. *Biochem. J.* **414**, 1–18 (2008).
- Chen, L., Zhang, J., Yang, R. & Feng, L. Glucokinase activator dorzagliatin (HMS5552) regulates GLP-1 release in T2D patients and is synergistic with sitagliptin and empagliflozin in optimizing beta-cell function. *Diabetes* **70**, 117–LB (2021).
- Li, C. et al. Regulation of glucagon secretion in normal and diabetic human islets by γ-hydroxybutyrate and glycine. *J. Biol. Chem.* **288**, 3938–3951 (2013).
- Hauesler, R. A. et al. Decreased expression of hepatic glucokinase in type 2 diabetes. *Mol. Metab.* **4**, 222–226 (2014).
- Froguel, P. et al. Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. *N. Engl. J. Med.* **328**, 697–702 (1993).
- Xu, H. et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of novel glucokinase activator HMS5552: results from a first-in-human single ascending dose study. *Drug Des. Devel. Ther.* **10**, 1619–1626 (2016).
- Zhu, X. X. et al. Dorzagliatin (HMS5552), a novel dual-acting glucokinase activator, improves glycaemic control and pancreatic β-cell function in patients with type 2 diabetes: a 28-day treatment study using biomarker-guided patient selection. *Diabetes Obes. Metab.* **20**, 2113–2120 (2018).
- Zhu, D. L. et al. Dorzagliatin monotherapy in Chinese patients with type 2 diabetes: a dose-ranging, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Diabetes Endocrinol.* **6**, 627–636 (2018).
- Bonadonna, R. C. et al. Piragliatin (RO4389620), a novel glucokinase activator, lowers plasma glucose both in the postabsorptive state and after a glucose challenge in patients with type 2 diabetes mellitus: a mechanistic study. *J. Clin. Endocrinol. Metab.* **95**, 5028–5036 (2010).
- Grimsby, J. et al. Allosteric activators of glucokinase: potential role in diabetes therapy. *Science* **301**, 370–373 (2003).
- Matschinsky, F. M. Assessing the potential of glucokinase activators in diabetes therapy. *Nat. Rev. Drug Discov.* **8**, 399–416 (2009).
- Zhi, J. & Zhai, S. Effects of piragliatin, a glucokinase activator, on fasting and postprandial plasma glucose in patients with type 2 diabetes mellitus. *J. Clin. Pharmacol.* **56**, 231–238 (2016).
- Wilding, J. P., Leonsson-Zachrisson, M., Wessman, C. & Johnsson, E. Dose-ranging study with the glucokinase activator AZD1656 in patients with type 2 diabetes mellitus on metformin. *Diabetes Obes. Metab.* **15**, 750–759 (2013).
- Kiyosue, A., Hayashi, N., Komori, H., Leonsson-Zachrisson, M. & Johnsson, E. Dose-ranging study with the glucokinase activator AZD1656 as monotherapy in Japanese patients with type 2 diabetes mellitus. *Diabetes Obes. Metab.* **15**, 923–930 (2013).
- Amin, N. B. et al. Two dose-ranging studies with PF-04937319, a systemic partial activator of glucokinase, as add-on therapy to metformin in adults with type 2 diabetes. *Diabetes Obes. Metab.* **17**, 751–759 (2015).
- Katz, L. et al. AMG 151 (ARRY-403), a novel glucokinase activator, decreases fasting and postprandial glycaemia in patients with type 2 diabetes. *Diabetes Obes. Metab.* **18**, 191–195 (2016).
- Meininger, G. E. et al. Effects of MK-0941, a novel glucokinase activator, on glycemic control in insulin-treated patients with type 2 diabetes. *Diabetes Care* **34**, 2560–2566 (2011).
- Chen, L., Shan, Y., Jin, X. & Lv, X. Dorzagliatin differentiates from early generation of glucokinase activators: an enzyme kinetics study. *Diabetes* **68**, 1151–P (2019).
- SEED Study Group. Dorza gliatin in drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat. Med.* (in the press).

29. Chen, L., Zhao, G., Ren, S., Zhang, Y. I. & Du, D. No drug–drug interaction between dorzagliatin and metformin in type 2 diabetes patients. *Diabetes* **67**, 2310–PUB (2018).
30. Yang, W. & Weng, J. Early therapy for type 2 diabetes in China. *Lancet Diabetes Endocrinol.* **2**, 992–1002 (2014).
31. Sharma, R. et al. Metabolites in safety testing assessment in early clinical development: a case study with a glucokinase activator. *Drug Metab. Dispos.* **42**, 1926–1939 (2014).
32. Study to Evaluate the Safety and Efficacy of PB-201 in Treatment-naive Patients With Type 2 Diabetes Mellitus. <https://www.clinicaltrials.gov/ct2/show/NCT05102149?term=PB201&draw=2&rank=2> (2021).
33. MedDRA Maintenance and Support Services Organization. Introductory Guide to MedDRA Version 23.0. <http://www.meddra.org/how-to-use/support-documentation> (2022).

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## Methods

**Trial design.** DAWN is a phase 3 trial conducted at 73 sites in China that enrolled patients with T2D experiencing inadequate glycemic control with metformin alone. The trial included a 2-week screening period, a 4-week single-blind placebo run-in period, a 24-week double-blind placebo-controlled treatment period, an extended 28-week open-label treatment period and a 1-week safety follow-up period (Extended Data Fig. 1).

**Patients.** Patients were recruited at the study site by investigators. The patients were required to sign an informed consent form before participating in any study procedures. Afterwards, the patients were screened for eligibility. Patients were not paid for taking part in the study, but they were compensated for travel to the site visit and blood draw at the site. During the study, patients were paid for completing different procedures at each visit. If the patients suffer any trial-related injury during the trial period, they can receive treatment at the study hospital, and the sponsor will cover the relevant medical costs as well as financial compensation as defined in relevant laws and regulations of China. Individuals (aged 18–75 years) were included in the trial if they were diagnosed with T2D; underwent diet and exercise interventions; were receiving stable daily doses of metformin (a minimum of 1,500 mg per day) for at least 12 weeks before screening; had an HbA1c level of 7.5–10.0% and a BMI of 18.5–35.0 kg m<sup>-2</sup> at screening; were willing to conduct self-monitoring of blood glucose; and were willing to provide the written informed consent form and comply with the study protocol.

The exclusion criteria were as follows: any previous anti-diabetic treatment other than metformin within the previous 12 weeks before screening; previous insulin treatment for more than 30 days within 1 year before screening; severe hypoglycemia without cause within the previous 3 months and frequent hypoglycemia occurring more than three times within the previous month; a fasting C-peptide level of less than 0.81 ng ml<sup>-1</sup> (normal range, 0.81–3.85 ng ml<sup>-1</sup>) at screening; a medical history of diabetic ketoacidosis, diabetes lactic acidosis or hyperosmotic non-ketotic diabetic coma; and clinically diagnosed with type 1 diabetes or diabetes caused by pancreatic damage or other special types of diabetes. Medical history and concomitant disease-related exclusion criteria were as follows: major cardio-cerebrovascular diseases within 6 months before screening; unstable or rapidly progressive kidney disease; active liver diseases; psychiatric diseases; hemoglobinopathies and immunocompromise; any type of malignancy; any endocrine system diseases or unstable immune diseases that need medical interventions and were determined by the investigator as not being suitable for this study; history of drug abuse; received oral or injected corticosteroids treatment within 1 year before screening; and alcohol intake of more than two units per day or more than 14 units per week. Physical examination and laboratory results-related exclusion criteria were alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5× the upper limit of normal (ULN); serum total bilirubin (TBil) level >1.5× the ULN; serological evidence of hepatitis virus infection at screening; estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>-2</sup> at screening; TG >5.7 mmol L<sup>-1</sup> at screening; anemia of any cause; abnormal laboratory or electrocardiogram results that may interfere with the safety evaluation; uncontrolled hypertension to anti-hypertensive treatment with stable doses for at least 4 weeks at screening; and any accompanied disease, treatment or participant status that may impede completion of the whole study or potentially affect the interpretation of efficacy and safety data.

**Trial procedures.** During the run-in period, all patients were treated with metformin (Glucophage, immediate-release hydrochloride tablets, 1,500 mg per day, provided by the sponsor) as the baseline therapy. The patients were advised to maintain their original dosage regimen of metformin 2–3 times per day for a total of 1,500 mg. The patients who received a dose of metformin >1,500 mg per day before entering the study were required to reduce the dose to 1,500 mg per day. After the run-in period, eligible patients were randomly assigned in a 1:1 ratio to receive either 75 mg of dorzagliatin BID and metformin (1,500 mg per day) or placebo BID and metformin (1,500 mg per day) for 24 weeks on a background of a diet and exercise regimen. Then, all patients received 75 mg of dorzagliatin BID and metformin (1,500 mg per day) treatment for 28 weeks.

At week 3 of the 4-week run-in period, the patients were reevaluated before randomization to confirm eligibility. Eligibility criteria included an HbA1c level of 7.5–10.0% and an FPG level of 126.0–239.4 mg dl<sup>-1</sup> at randomization. Diet and exercise counseling was provided throughout the experiment. Randomization and drug dispensing were performed with an interactive web response system (IWRS) (Medidata RAVE RTSM 2020.3.2). A stratified randomization method with the permuted block randomization algorithm was used. The blocks were dynamically allocated to each site and stratum from the randomization list. A unique ID number was provided by the vendor and marked on the drug box. Through central randomization, the randomization codes were generated by the IWRS system based on stratification factors (T2D disease duration ≤3 years or >3 years and HbA1c level ≤8.5% or >8.5% at randomization) and the block size. During the double-blind treatment, the random allocation sequences were concealed from the patients, investigators and other study members until week 24, and the blinding was maintained during the whole 52 weeks of treatment. The placebo tablets had the same size, color, smell and appearance as the active drug tablets.

**Efficacy endpoints.** The primary efficacy endpoint was the change in HbA1c level from baseline to week 24. Key secondary efficacy endpoints included the changes in 2h-PPG and FPG levels from baseline to week 24, HbA1c level at each visit (except week 24) and the percentage of patients who reached an HbA1c level of <7.0% at week 24. Additional efficacy endpoints included the changes in HOMA2-β (an index of β-cell function) and HOMA2-IR (an index of insulin resistance) from baseline. A complete list of other efficacy endpoints is provided in the statistical analysis plan in the supplementary materials. During the study, HbA1c and FPG levels were measured and evaluated at each visit from visits 4–15. At visits 4, 7, 10 and 15, 2h-PPG levels were measured using a standardized mixed-meal tolerance test (MMTT).

**Safety endpoints.** Safety assessments were performed at each study visit. Blood and urine samples were collected at each visit. Adverse Events (AEs) and Serious Adverse Events (SAEs) were assessed throughout the trial. Hypoglycemic episodes were classified according to American Diabetes Association definitions. Vital signs and clinical laboratory test results were assessed, and physical examinations were performed. All laboratory tests were conducted in the central laboratory. All samples were collected at the site.

**Trial oversight.** The trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and laws and regulations in China. The study protocol was amended once during the study. The important changes to the protocol, which mainly involve exclusion criteria and randomization criteria, are listed as follows: adjusted to fasting C-peptide <0.81 ng ml<sup>-1</sup> (0.27 nmol L<sup>-1</sup>) at screening; short-term external use of corticosteroids treatment within 1 year at screening was permissible; inhaled glucocorticoid treatment was unacceptable; stable coronary heart disease was allowed; exclusion and randomization criteria related to blood pressure and anti-hypertensive drugs were redefined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg at screening or patients who added/changed anti-hypertensive drugs or adjusted dose within 4 weeks before screening; 12-lead electrocardiogram was added to visit 3 as a pre-randomization criterion to ensure smooth conduct of the study; a visit window period of ±3 days for visit 2 was added to match actual operational needs; clarified that all blood samples were collected in fasting status except for MMTT 30 minutes and 120 minutes; 30-minute (±3 minutes were allowed) testing point for the MMTT was added to optimize the study protocol; clarified that the blood sampling time (MMTT, 120 minutes) for pharmacokinetics was before taking study medications; and the rule that patients need not to be in fasting status at visit 2 was removed for compliance. Minor protocol revisions involve wording, consistency and accuracy. The trial protocol and amendments were approved by the local ethics committees of all study sites: China-Japan Friendship Hospital, Beijing, China; Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China; The First People's Hospital of Changde City, Changde, China; Jinan Central Hospital Affiliated to Shandong First Medical University, Jinan, China; Cangzhou People's Hospital, Cangzhou, China; Peking Union Medical College Hospital, Beijing, China; The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, China; The Affiliated Hospital of Qingdao University, Qingdao, China; Qingdao Central Hospital, Qingdao, China; Chenzhou First People's Hospital, Chenzhou, China; The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; Tongji Hospital of Tongji University, Shanghai, China; The First Affiliated Hospital of Kunming Medical University, Kunming, China; The First Bethune Hospital of Jilin University, Changchun, China; Huzhou Central Hospital, Huzhou, China; The Affiliated Hospital of Jiangsu University, Zhenjiang, China; Nanjing First Hospital, Nanjing, China; The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; Inner Mongolia Baogang Hospital, Baotou, China; The First People's Hospital of Yue Yang, Yueyang, China; Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China; Jiangxi Pingxiang People's Hospital, Pingxiang, China; Jiangxi Provincial People's Hospital, Nanchang, China; The First People's Hospital of Shunde, Foshan, China; Chongqing General Hospital, Chongqing, China; Qinghai University Affiliated Hospital, Xining, China; Luoyang Central Hospital, Luoyang, China; General Hospital of Ningxia Medical University, Yinchuan, China; The General Hospital of Xuzhou City Mining Group, Xuzhou, China; Shanghai Pudong New Area People's Hospital, Shanghai, China; Beijing Friendship Hospital Pinggu Campus, Capital Medical University, Beijing, China; Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Baotou Central Hospital, Baotou, China; West China Hospital of Sichuan University, Chengdu, China; The 960th Hospital of the PLA Joint Logistics Support Force, Jinan, China; Yiyang Central Hospital, Yiyang, China; Yangpu Hospital, Tongji University, Shanghai, China; The First Affiliated Hospital of Anhui Medical University, Hefei, China; Taihe Hospital, Hubei University of Medicine, Shiyan, China; The First Hospital of China Medical University, Shenyang, China; Southern Medical University Nanfang Hospital, Guangzhou, China; The Central Hospital of Wuhan, Wuhan, China; The Affiliated Hospital of Guizhou Medical University, Guiyang, China; Anhui Provincial Hospital, Hefei, China; The First Affiliated Hospital of Bengbu Medical College, Bengbu, China; Huadong Hospital Affiliated to Fudan University, Shanghai, China; Jiangsu Province Hospital, Nanjing, China; Jining No. 1 People's

Hospital, Jining, China; Tianjin People's Hospital, Tianjin, China; The First Hospital of Qiqihar, Qiqihar, China; Jilin Central General Hospital, Jilin, China; Third People's Hospital of Yunnan Province, Kunming, China; Peking University First Hospital, Beijing, China; Ningbo First Hospital, Ningbo, China; The Affiliated Hua'an No. 1 People's Hospital of Nanjing Medical University, Hua'an, China; Shanghai Tenth People's Hospital, Shanghai, China; Emergency General Hospital, Beijing, China; The First Affiliated Hospital of Hainan Medical University, Haikou, China; Peking University Shougang Hospital, Beijing, China; Qinghai Provincial People's Hospital, Xining, China; Hainan General Hospital, Haikou, China; Liuzhou People's Hospital, Liuzhou, China; Yijishan Hospital, The First Affiliated Hospital of Wannan Medical University, Wuhu, China; The Second People's Hospital of Hua'an, Hua'an, China; Jiangsu Taizhou People's Hospital, Taizhou, China; Zhejiang Hospital, Hangzhou, China; Aerospace Center Hospital, Beijing, China; Yanbian University Hospital, Yanji, China; The Third Affiliated Hospital of Southern Medical University, Guangzhou, China; Beijing Luhe Hospital Affiliated to Capital Medical University, Beijing, China; Shanghai East Hospital, Tongji University, Shanghai, China; and Zhongshan Hospital, Fudan University, Shanghai, China. All patients provided written informed consent before trial entry. The trial was conducted in accordance with Chinese Diabetes Society guidelines, which require physicians to educate and strictly enforce improved exercise and dietary control and self-monitoring of blood glucose levels (at least two times per week) while treating patients with T2D.

**Statistical analyses.** We hypothesized that dorzagliatin would show superiority to placebo in decreasing HbA1c levels in patients after 24 weeks of treatment. For the primary endpoint HbA1c levels, we calculated that a total sample size of 750 patients would provide the trial with 95.4% power to detect a difference of 0.4% between the dorzagliatin and metformin group and the placebo and metformin group in a 1:1 ratio of allocation at a two-sided significance level of 0.05, assuming a standard deviation (s.d.) of 1.5%. The FAS included all randomized patients who took at least one dose of the study drug and completed at least one post-treatment measurement of the primary endpoint during the double-blind treatment period. All major protocol deviations were reviewed in the blind data review meeting to determine whether a participant with any major protocol deviations should be excluded from the per-protocol set (PPS). The safety set (SS) included all randomized patients who took at least one dose of the study drug. Because this trial included only one confirmatory hypothesis test—that is, to test the null hypothesis of no difference in the primary endpoint between the dorzagliatin and metformin and placebo and metformin groups—no adjustment for multiple comparisons was needed.

The primary analysis method for the primary endpoint in the FAS was a mixed model for repeated measures (MMRM) without missing value imputation, which included treatment group, scheduled visit, the interaction of treatment group with the scheduled visit, pooled site, duration of diabetes ( $\leq 3$  years or  $> 3$  years) and baseline HbA1c levels as fixed effects. In the MMRM, data collected after the initiation of prohibited anti-diabetic medications were handled as missing data. The least-squares (LS) means of each treatment group, the ETD between the dorzagliatin and metformin and placebo and metformin groups and its 95% CI were calculated. A sensitivity analysis of the primary endpoint was performed in the FAS and an analysis of covariance (ANCOVA) model with factors of treatment group, pooled site, duration of diabetes ( $\leq 3$  years or  $> 3$  years) and baseline HbA1c levels. In the ANCOVA model, missing values were imputed using the method of last observation carried forward (LOCF), which was applied after excluding data collected after the initiation of administering prohibited anti-diabetic medications. Another sensitivity analysis of the primary endpoint was performed using the same MMRM in the PPS. Primary endpoint data that were missing due to the inconvenience of on-site visits during the Coronavirus Disease 2019 epidemic (21 patients, including 13 patients in the dorzagliatin and metformin group and eight patients in the placebo and metformin group) were processed using the methods described in the statistical analysis plan. Then, a corresponding sensitivity analysis was performed using the same method as described in the primary analysis.

The secondary efficacy endpoints, including 2h-PPG, FPG and HbA1c levels at each visit (except week 24), were assessed using the same MMRM for the primary endpoint. Another secondary efficacy endpoint—that is, the percentage of patients who reached an HbA1c level of  $< 7.0\%$ —was estimated in the FAS based on the data imputed with the LOCF approach. The ORs and 95% CIs between the two treatment groups were estimated using the logistic regression model with the factors of the treatment group, pooled site, interaction of the treatment group with the pooled site (interaction effect removed from the model if not significant at a two-sided  $\alpha$  level of 0.1), duration of diabetes ( $\leq 3$  years or  $> 3$  years) and baseline HbA1c level. Exploratory efficacy endpoints of the change from baseline in HOMA2- $\beta$  and HOMA2-IR were analyzed in the FAS using an ANCOVA model with the factors treatment group, pooled site, duration of diabetes ( $\leq 3$  years or  $> 3$  years) and baseline level of the analyzed variable. A post hoc analysis was conducted to analyze an exploratory efficacy endpoint of the composite endpoint (HbA1c  $< 7.0\%$  without hypoglycemia and no weight gain), which was estimated based on the data imputed by the LOCF approach in the FAS. The OR and 95% CI between two treatment groups were estimated using the logistic regression model with categorical independent variables of the treatment group, pooled site, duration of diabetes ( $\leq 3$  years or  $> 3$  years), interaction of the treatment group with

the pooled site (interaction effect removed from the model if not significant at a two-sided  $\alpha$  level of 0.1) and a continuous independent variable of baseline HbA1c level. Furthermore, as another post hoc analysis to explore the in-group reduction in HbA1c from baseline at week 24 and week 52, paired *t*-tests based on observed measurements were carried out to compare HbA1c between at baseline and at week 24 or week 52 in each of dorzagliatin and placebo groups.

The incidence of treatment-emergent AEs between the first intake of the double-blind study drug and the 7th day after the last dose was summarized by the treatment group and compared between the two groups. The incidence of hypoglycemic events was also summarized by the treatment group and compared between treatment groups. The commercially available software Electronic Data Capture (Medidata RAVE, Classic Rave version 2018.2.4) was used for clinical trial patient data collection. Additional details regarding the statistical analysis are provided in the statistical analysis plan in the supplementary materials, and SAS software (SAS Institute, version 9.4) was used for analyses.

**Reporting Summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

## Data availability

Data from these analyses in the DAWN study cannot be made publicly available due to the sponsor's contractual obligations. We encourage researchers or parties interested in collaboration for non-commercial use to apply to the corresponding author (lichen@huamedicine.com). Applications should outline specifically what data they are interested in receiving and how the data will be used. The use of data must also comply with the requirements of the Human Genetics Resources Administration of China and other country- or region-specific regulations. All data shared will be de-identified and will be made available 2 years after the date of publication. A signed data access agreement with the sponsor is required before accessing the shared data. The study protocol and statistical analysis plan are provided with the paper.

## Acknowledgements

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## Author contributions

W.Y. and L.C. led the design, conduct and analysis of the clinical study and the development of the manuscript. As study consultants, D.Z. and X.L. contributed to the protocol design, data analysis and manuscript draft. The trial was designed and overseen by the authors who are employees of the sponsor (Hua Medicine), with input from selected site investigators. The site investigators collected the data, and the sponsor performed the data analyses. All authors were involved in interpreting the data and in ensuring the accuracy and completeness of the data and the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript with assistance from an independent medical writer funded by the sponsor. The manuscript was subsequently revised and approved by all authors, who agreed to submit the manuscript for publication.

## Competing interests

L.Chen, Y.Zhao and Y.Zhang are employees of Hua Medicine. W.Yang, D.Zhu and X.Li have served on the Diabetes Advisory Board for Hua Medicine. The remaining authors declare no competing interests.

## Additional information

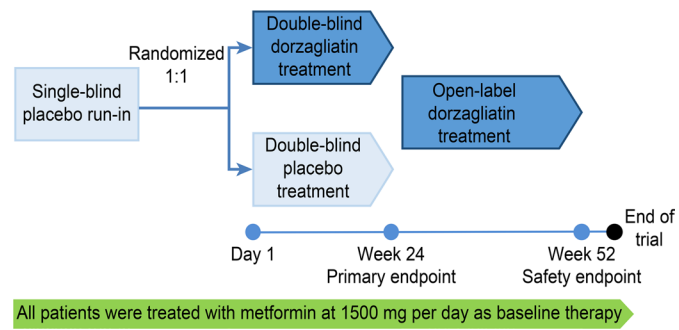
**Extended data** is available for this paper at <https://doi.org/10.1038/s41591-022-01803-5>.

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41591-022-01803-5>.

**Correspondence and requests for materials** should be addressed to Dalong Zhu, Xiaoying Li or Li Chen.

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**Extended Data Fig. 1** | DAWN study design.

## Reporting Summary

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*Give  $P$  values as exact values whenever suitable.*
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### Software and code

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**Data collection** Commercially available software Electronic Data Capture (EDC) (Medidata RAVE, Classic Rave version 2018.2.4) was used for clinical trial patient data collection. Randomization and drug dispensing were performed with an interactive web response system (IWRS) (Medidata RAVE RTSM 2020.3.2).

**Data analysis** SAS software (SAS Institute Inc., Cary, N.C., version 9.4) was used for analyses. Data were computed using the HOMA2 Calculator version 2.2.3: <https://www.dtu.ox.ac.uk/homacalculator/download.php>.

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Data from these analyses in the DAWN study cannot be made publicly available due to the sponsor's contractual obligations. We encourage researchers or parties interested in collaboration for non-commercial use to apply to the corresponding author (lichen@huamedicine.com). Applications should outline specifically what data they are interested in receiving and how the data will be used; the use of data must also comply with the requirements of the Human Genetics Resources Administration of China and other country- or region-specific regulations. All data shared will be de-identified and will be made available 2 years after the date of

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## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We hypothesized that dorzagliatin would show superiority to placebo in decreasing HbA1c levels in patients after 24 weeks of treatment. For the primary endpoint HbA1c levels, we calculated that a total sample size of 750 patients would provide the trial with 95.4% power to detect a difference of 0.4% between the dorzagliatin and metformin group and the placebo and metformin group in a 1:1 ratio of allocation at a 2-sided significance level of 0.05, assuming a standard deviation (SD) of 1.5%.
Data exclusions	The full-analysis set included all randomized patients who took at least one dose of the study drug and had at least one posttreatment measurement of the primary endpoint during the double-blind treatment period (16 randomized patients were excluded from the full-analysis set: 15 owing to lack of efficacy assessments and 1 owing to no drugs taken after randomization).
Replication	This Phase 3 RCT replicates previous findings in a previously published controlled Phase 2 trial (Zhu D 2018).
Randomization	At week 3 of the 4-week run-in period, the patients were reevaluated before randomization to confirm eligibility. Eligibility criteria included an HbA1c level of 7.5 to 10.0% and an FPG level of 126.0 to 239.4 mg/dl at randomization. Diet and exercise counseling was provided throughout the experiment. Randomization and drug dispensing were performed with an interactive web response system (IWRS) (Medidata RAVE RTSM 2020.3.2). A stratified randomization method with the permuted block randomization algorithm was used. The blocks were dynamically allocated to each site and stratum from the randomization list. A unique ID number was provided by the vendor and marked on the drug box. Through central randomization, the randomization codes were generated by the IWRS system based on stratification factors (T2D disease duration $\leq 3$ years or $> 3$ years and HbA1c level $\leq 8.5\%$ or $> 8.5\%$ at randomization) and the block size.
Blinding	During the double-blind treatment, the random allocation sequences were concealed from the patients, investigators, and other study members until week 24. And the blinding was maintained during the whole 52 weeks of treatment. The placebo tablets had the same size, color, smell and appearance as the active drug tablets.

## Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	<i>Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).</i>
Research sample	<i>State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.</i>
Sampling strategy	<i>Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.</i>
Data collection	<i>Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.</i>
Timing	<i>Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.</i>
Data exclusions	<i>If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.</i>
Non-participation	<i>State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.</i>
Randomization	<i>If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.</i>



# Ecological, evolutionary & environmental sciences study design

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Study description	Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.
Research sample	Describe the research sample (e.g. a group of tagged <i>Passer domesticus</i> , all <i>Stenocereus thurberi</i> within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.
Sampling strategy	Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.
Data collection	Describe the data collection procedure, including who recorded the data and how.
Timing and spatial scale	Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken
Data exclusions	If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.
Reproducibility	Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.
Randomization	Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.
Blinding	Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.
Did the study involve field work?	<input type="checkbox"/> Yes <input type="checkbox"/> No

## Field work, collection and transport

Field conditions	Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).
Location	State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).
Access & import/export	Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).
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### Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
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### Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Antibodies

Antibodies used	<i>Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.</i>
Validation	<i>Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.</i>

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Cell line source(s)	<i>State the source of each cell line used.</i>
Authentication	<i>Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.</i>
Mycoplasma contamination	<i>Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.</i>
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Specimen provenance	<i>Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information).</i>
Specimen deposition	<i>Indicate where the specimens have been deposited to permit free access by other researchers.</i>
Dating methods	<i>If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.</i>
<input type="checkbox"/> Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.	
Ethics oversight	<i>Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.</i>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Animals and other organisms

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Laboratory animals	<i>For laboratory animals, report species, strain, sex and age OR state that the study did not involve laboratory animals.</i>
Wild animals	<i>Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.</i>
Field-collected samples	<i>For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.</i>
Ethics oversight	<i>Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.</i>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Human research participants

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Population characteristics	Among the 767 randomized patients, 475 (62%) were male and 292 (38%) were female. The average age of the study patients was 54.5±9.6 years, and the average disease duration was 71.5±55.8 months. The patients had an average body mass index (BMI) of 25.9±3.1 kg/m <sup>2</sup> and a mean HbA1c value of 8.3±0.6% at baseline. The demographic and baseline characteristics were similar between the two groups (Table 1).
Recruitment	Patients were recruited at the study site by investigators. The patients were required to sign an informed consent form prior to participating in any study procedures. Patients were recruited from October 11, 2017, to August 30, 2019, and the last patient visit was conducted on August 31, 2020. Of the 1721 patients screened, 767 eligible patients were randomly assigned to one of the two treatment groups; 382 patients were assigned to receive dorzagliatin (75 mg twice a day) and metformin (1500 mg daily), and 385 patients were assigned to receive placebo and metformin (1500 mg daily) (Figure 1). In total, 766

patients took at least one dose of the study drug and were included in the safety analysis set; 751 patients completed at least one post-randomization measurement and were included in the full-analysis set (FAS).

## Ethics oversight

The trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and laws and regulations in China. The study protocol was amended once during the study. The important changes to the protocol, which mainly involves exclusion criteria and randomization criteria are listed as follows: adjusted to fasting C-peptide <0.81 ng/ml (0.27 nmol/L) at screening; short-term external use of corticosteroids treatment within 1 year at screening was permissible; inhaled glucocorticoid treatment was unacceptable; stable coronary heart disease was allowed; exclusion and randomization criteria related to blood pressure and antihypertensive drugs were redefined as systolic blood pressure  $\geq$  160 mmHg or diastolic blood pressure  $\geq$  100 mmHg at screening, or who added/changed antihypertensive drugs or adjusted dose within 4 weeks before screening; 12-lead electrocardiogram was added to Visit 3 as a pre-randomization criterion to ensure smooth conduct of the study; a visit window period of  $\pm$  3 days for Visit 2 was added to match actual operational needs; clarified that all blood samples were collected in fasting status except for MMTT 30-min and 120-min; 30-minute ( $\pm$ 3 minutes were allowed) testing point for the MMTT was added to optimize the study protocol; clarified the blood sampling time (MMTT 120 min) for pharmacokinetics was before taking study medications; the rule that patients need not to be in fasting status at Visit 2 was removed for compliance. Minor protocol revisions involve wording, consistency, and accuracy. The trial protocol and amendments were approved by the local ethics committees of all study sites: China-Japan Friendship Hospital, Beijing, China; Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China; The First People's Hospital of Changde City, Changde, China; Central Hospital Affiliated to Shandong First Medical University, Jinan, China; Cangzhou People's Hospital, Cangzhou, China; Peking Union Medical College Hospital, Beijing, China; The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; The Affiliated Hospital of Qingdao University, Qingdao, China; Qingdao Central Hospital, Qingdao, China; Chenzhou First People's Hospital, Chenzhou, China; The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; Tongji Hospital of Tongji University, Shanghai, China; The First Affiliated Hospital of Kunming Medical University, Kunming, China; The First Bethune Hospital of Jilin University, Changchun, China; Huzhou Central Hospital, Huzhou, China; The Affiliated Hospital of Jiangsu University, Zhenjiang, China; Nanjing First Hospital, Nanjing, China; The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; Inner Mongolia Baogang Hospital, Baotou, China; The First People's Hospital of Yue Yang, Yueyang, China; Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China; Jiangxi Pingxiang People's Hospital, Pingxiang, China; Jiangxi Provincial People's Hospital, Nanchang, China; The First People's Hospital of Shunde, Foshan, China; Chongqing General Hospital, Chongqing, China; Qinghai University Affiliated Hospital, Xining, China; Luoyang Central Hospital, Luoyang, China; General Hospital of Ningxia Medical University, Yinchuan, China; The General Hospital of Xuzhou City Mining Group, Xuzhou, China; Shanghai Pudong New Area People's Hospital, Shanghai, China; Beijing Pinggu Hospital, Beijing, China; Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Baotou Central Hospital, Baotou, China; West China Hospital of Sichuan University, Chengdu, China; The 960th Hospital of the PLA Joint Logistics Support Force, Jinan, China; Yiyang Central Hospital, Yiyang, China; Yangpu Hospital, Tongji University, Shanghai, China; The First Affiliated Hospital of Anhui Medical University, Hefei, China; Taihe Hospital, Shiyan, China; The First Hospital of China Medical University, Shenyang, China; Southern Medical University Nanfang Hospital, Guangzhou, China; The Central Hospital of Wuhan, Wuhan, China; The Affiliated Hospital of Guizhou Medical University, Guiyang, China; Anhui Provincial Hospital, Hefei, China; The First Affiliated Hospital of Bengbu Medical College, Bengbu, China; Huadong Hospital Affiliated to Fudan University, Shanghai, China; Jiangsu Province Hospital, Nanjing, China; Jining No. 1 People's Hospital, Jining, China; Tianjin People's Hospital, Tianjin, China; The First Hospital of Qiqihar, Qiqihar, China; Jilin Central General Hospital, Jilin, China; Third People's Hospital of Yunnan Province, Kunming, China; Peking University First Hospital, Beijing, China; Ningbo First Hospital, Ningbo, China; The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University, Huai'an, China; Shanghai Tenth People's Hospital, Shanghai, China; Emergency General Hospital, Beijing, China; The First Affiliated Hospital of Hainan Medical University, Haikou, China; Peking University Shougang Hospital, Beijing, China; Qinghai Provincial People's Hospital, Xining, China; Hainan General Hospital, Haikou, China; Liuzhou People's Hospital, Liuzhou, China; The First Affiliated Hospital of Wannan Medical University, Wuhu, China; The Second People's Hospital of Huai'an, Huai'an, China; Jiangsu Taizhou People's Hospital, Taizhou, China; Zhejiang Hospital, Hangzhou, China; Aerospace Center Hospital, Beijing, China; Yanbian University Hospital, Yanji, China; The Third Affiliated Hospital of Southern Medical University, Guangzhou, China; Beijing Luhe Hospital Affiliated to Capital Medical University, Beijing, China; Shanghai East Hospital, Tongji University, Shanghai, China; Zhongshan Hospital, Fudan University, Shanghai, China. All patients provided written informed consent before trial entry. The trial was conducted in accordance with the Chinese Diabetes Society guidelines, which require physicians to educate and strictly enforce improved exercise and dietary control and self-monitoring of blood glucose levels (at least two times/week) while treating patients with T2D.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

Study protocol

Data collection

Outcomes

at each visit. Adverse events and serious adverse events were assessed throughout the trial. Hypoglycemic episodes were classified according to the American Diabetes Association (ADA) definitions. Vital signs and clinical laboratory test results were assessed, and physical examinations were performed.

## Dual use research of concern

Policy information about [dual use research of concern](#)

### Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

- | No                       | Yes                      |
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### Experiments of concern

Does the work involve any of these experiments of concern:

- | No                       | Yes                      |
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## ChIP-seq

### Data deposition

- Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

#### Data access links

May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

#### Files in database submission

Provide a list of all files available in the database submission.

#### Genome browser session

(e.g. [UCSC](#))

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

### Methodology

#### Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

#### Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

#### Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

#### Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

#### Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

#### Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community

## Flow Cytometry

### Plots

Confirm that:

- The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- All plots are contour plots with outliers or pseudocolor plots.
- A numerical value for number of cells or percentage (with statistics) is provided.

### Methodology

Sample preparation

*Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*

Instrument

*Identify the instrument used for data collection, specifying make and model number.*

Software

*Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*

Cell population abundance

*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*

Gating strategy

*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

- Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

## Magnetic resonance imaging

### Experimental design

Design type

*Indicate task or resting state; event-related or block design.*

Design specifications

*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*

Behavioral performance measures

*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

### Acquisition

Imaging type(s)

*Specify: functional, structural, diffusion, perfusion.*

Field strength

*Specify in Tesla*

Sequence & imaging parameters

*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*

Area of acquisition

*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI

Used

Not used

### Preprocessing

Preprocessing software

*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*

Normalization

*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*

Normalization template

*Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*

Noise and artifact removal

*Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).*



Volume censoring

*Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.***Statistical modeling & inference**

Model type and settings

*Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).*

Effect(s) tested

*Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.*Specify type of analysis:  Whole brain  ROI-based  BothStatistic type for inference  
(See [Eklund et al. 2016](#))*Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.*

Correction

*Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).***Models & analysis**

n/a | Involved in the study

  Functional and/or effective connectivity  Graph analysis  Multivariate modeling or predictive analysis

Functional and/or effective connectivity

*Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).*

Graph analysis

*Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).*

Multivariate modeling and predictive analysis

*Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.*