


Efficacy and safety of dulaglutide monotherapy compared with glimepiride in Chinese patients with type 2 diabetes: Post-hoc analyses of a randomized, double-blind, phase III study

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Keywords

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ABSTRACT

Aims/Introduction: To investigate the efficacy/safety of dulaglutide once-weekly monotherapy versus glimepiride in Chinese patients with type 2 diabetes.

Materials and Methods: This was a post-hoc analysis of a Chinese randomized, double-blind, non-inferiority, phase III study. Patients ($n = 572$) with inadequate glycemic control received dulaglutide 1.5 mg ($n = 189$) or 0.75 mg ($n = 194$) once-weekly or glimepiride (1–3 mg/day; $n = 189$) for 26 weeks. The primary objective of the study was to investigate the non-inferiority of dulaglutide 1.5 mg versus glimepiride by the change from baseline to week 26 in glycated hemoglobin (non-inferiority margin 0.4%).

Results: Dulaglutide 1.5 mg and 0.75 mg were non-inferior ($P < 0.001$) and superior ($P \leq 0.002$) versus glimepiride for the change in glycated hemoglobin from baseline to week 26. The least-squares mean differences (95% confidence interval) versus glimepiride were dulaglutide 1.5 mg, -0.53% ($-0.74, -0.32$) and dulaglutide 0.75 mg, -0.32% ($-0.53, -0.12$). Significantly more patients attained glycated hemoglobin $<7.0\%$ at week 26 in the dulaglutide 1.5 mg (71.7%) versus the glimepiride (57.5%; $P = 0.005$) group. The decrease from baseline to week 26 in fasting blood glucose was significantly more pronounced in both the dulaglutide groups versus the glimepiride group ($P < 0.01$). The overall incidence and rate of hypoglycemia were lower in both of the dulaglutide groups versus the glimepiride group. At week 26, bodyweight had increased from baseline in the glimepiride group and decreased from baseline in both dulaglutide groups. The most frequent gastrointestinal drug-related adverse events with dulaglutide were diarrhea, abdominal distension, nausea and vomiting.

Conclusions: These findings support once-weekly dulaglutide monotherapy as a treatment for Chinese patients with early stage type 2 diabetes.

INTRODUCTION

Type 2 diabetes is becoming increasingly prevalent in China¹ and other East Asian countries². Recent International Diabetes Federation estimates show that nearly 11% of adults in China

have diabetes, and that more than half (53.6%) of these adults remain undiagnosed³. With increasing rates of obesity (driven by economic development and consequent lifestyle changes)¹, the prevalence and related economic burden of type 2 diabetes in China seems likely to further increase. Therefore, identifying treatment strategies that are effective for Chinese patients with type 2 diabetes is of clear importance.

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Dulaglutide is a long-acting human glucagon-like peptide-1 receptor agonist that has been approved as a once-weekly subcutaneous injection for the treatment of type 2 diabetes based on findings from the phase III AWARD (Assessment of Weekly Administration of dulaglutide in Diabetes) studies^{4–10}. Treatment with dulaglutide is associated with effective glycemic control, a relatively low rate of hypoglycemia, decreased bodyweight and the benefits of once-weekly dosing¹¹. In addition to being efficacious in combination with other therapies^{4–6,8–10}, dulaglutide monotherapy was found to significantly improve glycemic control (compared with metformin), and was well tolerated in the global, phase III, AWARD-3 study⁷. More recently, results from a phase III clinical study in East Asian patients with type 2 diabetes showed that dulaglutide monotherapy (1.5 and 0.75 mg) provided glycemic control superior to that provided by glimepiride (a commonly used oral antidiabetic drug in China¹²), and had favorable safety and tolerability¹³.

The aim of the present post-hoc analysis of the aforementioned phase III East Asian study¹³ was to assess the efficacy and safety of dulaglutide monotherapy (1.5 and 0.75 mg once-weekly) versus glimepiride in Chinese patients with inadequately controlled type 2 diabetes who were either naïve to or taking oral anti-hyperglycemic medication (OAM) as monotherapy.

METHODS

Study design

The post-hoc analyses of Chinese patients with type 2 diabetes were of a previously described¹³ randomized, multicenter, double-blind, phase III study carried out in China (29 sites), Taiwan and South Korea (ClinicalTrials.gov: NCT01644500).

Ethical review boards at each study site reviewed and approved the study protocol. The study was carried out as per the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Conference on Harmonization, Good Clinical Practices Guideline [E6], and applicable local laws and regulations.

All patients gave written informed consent before participating in the study.

Patients

All Chinese patients meeting the previously described inclusion and exclusion criteria¹³ were included in the post-hoc analyses. Key inclusion criteria included a body mass index ≥ 19 and ≤ 35 kg/m² and OAM-naïvety (with glycated hemoglobin [HbA1c] ≥ 7.0 and $\leq 10.5\%$ at screening) or discontinuation of OAM monotherapy for ≥ 3 months before screening (with HbA1c ≥ 6.5 and $\leq 10.0\%$ at screening). Key exclusion criteria included any prescription for incretin-based medications and treatment with insulin within 3 months before screening.

Treatment protocol

The study treatment protocol has been described in full previously¹³. Patients received subcutaneous dulaglutide 1.5 or

0.75 mg once-weekly, or oral glimepiride 1–3 mg/day for 26 weeks. Glimepiride dosing began at 1 mg/day, and was increased at week 4 to 2 mg/day and at week 8 to 3 mg/day, as tolerated.

Outcome measures

Efficacy

The study outcome measures have been described previously¹³. The primary and key secondary efficacy outcome measures were the change from baseline to week 26 in HbA1c for dulaglutide 1.5 mg versus glimepiride and dulaglutide 0.75 mg versus glimepiride, respectively. Other secondary efficacy outcomes at week 26 were: the proportion of patients who attained HbA1c < 7.0 or $\leq 6.5\%$; 7-point self-monitored blood glucose (SMBG) concentration profiles; fasting blood glucose (FBG) concentrations; blood glucose concentration excursions; and insulin sensitivity and β -cell function, as determined using updated homeostasis model assessment (per blood glucose, C-peptide and insulin levels).

Safety

As previously described¹³, safety outcomes included treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, serious adverse events, the incidence and the rate of hypoglycemia, bodyweight change, vital signs, laboratory tests, electrocardiograms, dulaglutide anti-drug antibodies (ADAs), and any allergic or hypersensitivity reactions.

Events that were considered definitive or possible acute pancreatitis were independently adjudicated by an expert committee.

All deaths/non-fatal cardiovascular adverse events were adjudicated by an external committee.

Statistical analysis

As previously described¹³, the study sample size was calculated based on a one-sided significance level of 0.025, a non-inferiority margin of 0.4% and a standard deviation (SD) of 1.3 for the change from baseline to week 26 in HbA1c. Approximately 789 patients were to be enrolled in the study.

A modified intention-to-treat population was used for the efficacy analyses, which comprised all patients with a baseline HbA1c reading and one or more post-baseline HbA1c reading, and who had received one or more dose of the study drug.

An as-treated population (the treatment patients actually received) was used for the safety analyses. The population included all patients who received one or more dose of the study drug.

The change from baseline to week 26 in HbA1c was analyzed using a mixed-model repeated measures analysis. Fixed effects were treatment, visit, treatment-by-visit interaction and pre-study treatment. The covariate was baseline HbA1c, and the random effect was patient. Missing data were not imputed. The treatment difference (dulaglutide 1.5 mg minus glimepiride) at week 26 was estimated using the corresponding 95%

confidence interval (CI) of the least-squares mean (LSM). Dulaglutide 1.5 mg was considered non-inferior to glimepiride if the upper bound of the 95% CI for the difference between treatments was $<0.4\%$. In the case where non-inferiority was achieved, the type 1 error rate was controlled at 0.025 using tree gatekeeping¹⁴. The superiority of dulaglutide 1.5 mg versus glimepiride, along with the non-inferiority and superiority of dulaglutide 0.75 mg versus glimepiride, was then assessed. As these were post-hoc analyses, no adjustments for multiplicity were made.

Secondary efficacy outcomes were analyzed by Fisher's exact test (proportion of patients attaining HbA1c targets), mixed-model repeated measures analysis for the primary efficacy outcome (FBG, 7-point SMBG profiles, BG excursions) or analysis of covariance (insulin sensitivity, β -cell function).

Demographics and baseline characteristics were analyzed by Fisher's exact test or an analysis of variance model for categorical and continuous data, respectively.

Safety outcomes were analyzed using descriptive statistics. Categorical data are summarized using counts and percentages. Continuous data are summarized using the mean, standard deviation and median.

For all comparisons, $P < 0.05$ was taken to show statistical significance.

RESULTS

Patient disposition/baseline characteristics

Of the 572 patients randomized (dulaglutide 1.5 mg [$n = 189$]; dulaglutide 0.75 mg [$n = 194$]; glimepiride [$n = 189$]), 50

(8.7%) discontinued the study and 522 (91.3%) completed study treatment (Figure 1).

Demographic and baseline clinical characteristics were similar across the three treatment groups (Table 1). The overall mean values for key variables at baseline were: HbA1c 8.0% (SD 1.0%); bodyweight, 69.8 kg (SD 11.1 kg); and duration of type 2 diabetes 3.6 years (SD 4.3 years). Slightly $>50\%$ of patients had a history of treatment with ≥ 1 OAM.

Efficacy

The LSM decrease in HbA1c from baseline to week 26 was significantly more pronounced in both of the dulaglutide groups (1.5 mg -1.46% , [standard error {SE}] 0.08%; 0.75 mg, -1.25% [SE 0.08%]) versus the glimepiride group (-0.92% [SE 0.08%]); both dulaglutide doses were non-inferior and superior to glimepiride in reducing HbA1c (all $P < 0.01$; Figure 2). The LSM difference in HbA1c versus glimepiride was -0.53% for dulaglutide 1.5 mg, and -0.32% for dulaglutide 0.75 mg at week 26. The change from baseline in HbA1c over time for each treatment group is summarized in Figure 3.

A significantly greater proportion of patients attained week 26 HbA1c targets of $<7.0\%$ and $\leq 6.5\%$ in the dulaglutide 1.5 mg group (71.7 and 57.1%) compared with the glimepiride group (57.5 and 40.9%, both $P < 0.01$; Figure 4). There was no significant difference in the proportion of patients attaining week 26 HbA1c targets between the dulaglutide 0.75 mg and glimepiride groups.

The LSM decrease in FBG from baseline to week 26 was significantly more pronounced in both of the dulaglutide groups

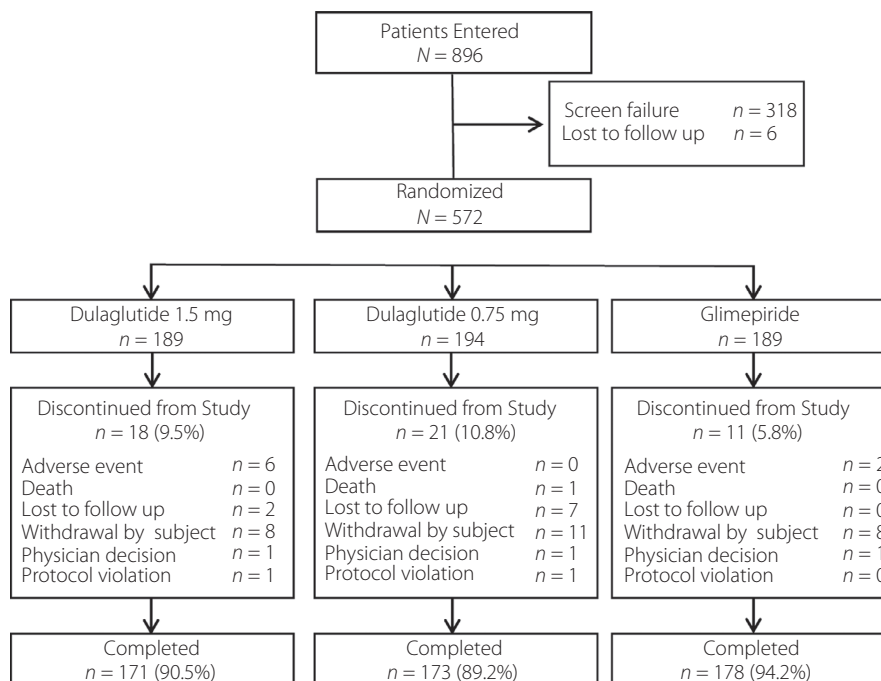


Figure 1 | Patient disposition.

Table 1 | Patient demographics and baseline clinical characteristics (modified intention-to-treat analysis set)

Variable	Dulaglutide 1.5 mg (n = 184)	Dulaglutide 0.75 mg (n = 186)	Glimepiride (n = 186)	Total (n = 556)
Male, n (%)	109 (59.2)	107 (57.5)	109 (58.6)	325 (58.5)
Age, years (mean ± SD)	52.8 ± 10.40	53.8 ± 9.83	52.7 ± 9.61	53.1 ± 9.95
<65 years, n (%)	167 (90.8)	163 (87.6)	172 (92.5)	502 (90.3)
≥65 years, n (%)	17 (9.2)	23 (12.4)	14 (7.5)	54 (9.7)
Bodyweight (kg)	69.7 ± 10.8	70.7 ± 12.0	69.1 ± 10.6	69.8 ± 11.1
BMI (kg/m ²)	25.5 ± 3.21	26.0 ± 3.34 [†]	25.3 ± 2.92	25.6 ± 3.17
HbA1c, % (mean ± SD)	8.0 ± 1.00	8.0 ± 1.01	7.9 ± 1.01	8.0 ± 1.00
<8.5%, n (%)	129 (70.1)	127 (68.3)	134 (72.0)	390 (70.1)
≥8.5%, n (%)	55 (29.9)	59 (31.7)	52 (28.0)	166 (29.9)
Duration of T2D (years)	4.0 ± 4.67	3.2 ± 4.00	3.6 ± 4.10 [‡]	3.6 ± 4.26
History of ≥1 previous OAM				
Yes, n (%)	97 (52.7)	96 (51.6)	99 (53.2)	292 (52.5)
Current alcohol use, n (%)	41 (22.3)	33 (17.7)	34 (18.4) [§]	108 (19.5)
Current tobacco use,* n (%)	64 (35.2) [¶]	41 (22.0)	49 (26.5) ^{††}	154 (27.8)
Systolic BP (mmHg)	129 ± 13.2	129 ± 13.9	128 ± 15.0	128 ± 14.0
Diastolic BP (mmHg)	79 ± 9.0	79 ± 9.4	78 ± 8.8	78 ± 9.1
Pulse rate (b.p.m.)	76 ± 10.1	75 ± 9.1	77 ± 9.6	76 ± 9.6

Data are presented as the mean ± standard deviation, except where indicated. * $P < 0.05$ based on Fisher's exact test. [†] $n = 185$; [‡] $n = 185$; [§] $n = 185$; [¶] $n = 182$; ^{††} $n = 185$. BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; OAM, oral antidiabetic medication; SD, standard deviation; T2D, type 2 diabetes.

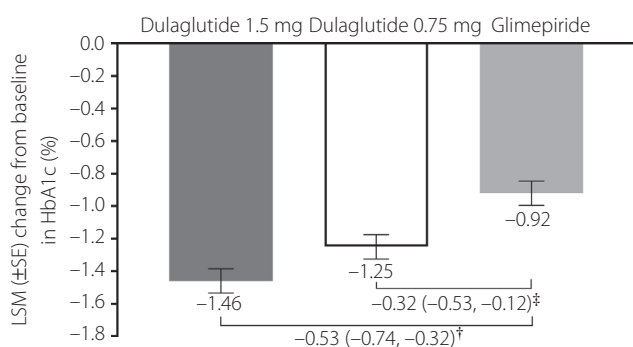


Figure 2 | Change in glycated hemoglobin (HbA1c) from baseline to week 26 in Chinese patients with type 2 diabetes who were treated with dulaglutide 1.5 mg, dulaglutide 0.75 mg or glimepiride. [†]Difference in least-squares mean (LSM; 95% confidence interval) between dulaglutide 1.5 mg and glimepiride. Dulaglutide 1.5 mg was non-inferior and superior to glimepiride (both $P < 0.001$). [‡]Difference in LSM (95% confidence interval) between dulaglutide 0.75 mg and glimepiride. Dulaglutide 0.75 mg was non-inferior ($P < 0.001$) and superior ($P = 0.002$) to glimepiride.

(1.5 mg, -2.29 mmol/L [SE 0.14 mmol/L]; 0.75 mg, -1.84 mmol/L, [SE 0.14 mmol/L]) compared with the glimepiride group (-1.41 mmol/L [SE 0.14 mmol/L], both $P < 0.05$; Figure 5).

At week 26, the magnitude of decrease at each assessment time in the 7-point SMBG profile was significantly more pronounced in the dulaglutide 1.5 mg group versus the glimepiride group ($P < 0.01$; Figure 6; Table S1). The daily LSM SMBG

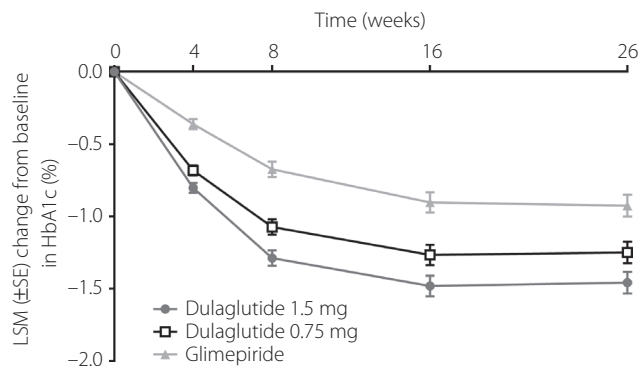


Figure 3 | Change in glycated hemoglobin (HbA1c) from baseline (last observation carried forward) over time in Chinese patients with type 2 diabetes who were treated with dulaglutide 1.5 mg, dulaglutide 0.75 mg or glimepiride. LSM, least-squares mean; SE, standard error.

decrease was also significantly more pronounced in the dulaglutide 1.5 mg group versus the glimepiride group (-2.94 mmol/L [SE 0.12 mmol/L] vs -1.90 mmol/L [SE 0.12 mmol/L]; $P < 0.001$). Decreases from baseline in all postprandial excursions were significantly more pronounced in the dulaglutide 1.5 mg group versus the glimepiride group (all $P < 0.05$). At week 26, the magnitude of decrease at the morning 2-h postprandial, midday 2-h postprandial and bedtime assessments was significantly more pronounced in the dulaglutide 0.75 mg group versus the glimepiride group (all $P < 0.05$; Figure 6; Table S1). The daily LSM SMBG decrease was significantly

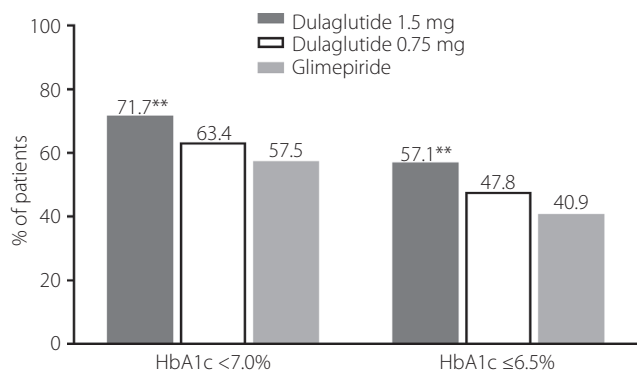


Figure 4 | Proportion (last observation carried forward) of Chinese patients with type 2 diabetes who attained glycated hemoglobin (HbA1c) targets at week 26 after treatment with dulaglutide 1.5 mg, dulaglutide 0.75 mg or glimepiride. ** $P < 0.01$ versus glimepiride.

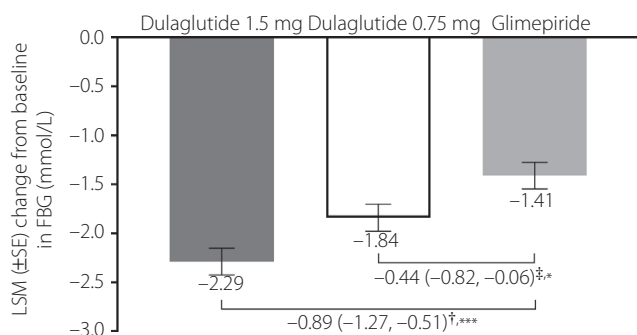


Figure 5 | Change in fasting blood glucose (FBG) from baseline to week 26 in Chinese patients with type 2 diabetes who were treated with dulaglutide 1.5 mg, dulaglutide 0.75 mg or glimepiride. †Difference in least-squares mean (LSM; 95% confidence interval) between dulaglutide 1.5 mg and glimepiride. ‡Difference in LSM (95% confidence interval) between dulaglutide 0.75 mg and glimepiride. * $P < 0.05$ versus glimepiride; *** $P < 0.001$ versus glimepiride. SE, standard error.

more pronounced in the dulaglutide 0.75 mg group versus the glimepiride group (-2.27 [SE 0.12] mmol/L vs -1.90 [SE 0.12] mmol/L; $P = 0.030$). The decrease from baseline in the midday 2-h excursion was significantly more pronounced in the dulaglutide 1.5 mg group versus the glimepiride group ($P = 0.022$; Table S1).

At week 26, the increase in C-peptide and insulin-based updated homeostasis model assessment for β -cell function was significantly more pronounced in the dulaglutide groups versus the glimepiride group (all $P < 0.001$; Table S2).

Safety

The incidence of TEAEs was similar among the dulaglutide and glimepiride treatment groups (Table 2). Overall, 61.6% of all patients reported one or more TEAE. The majority of events

were mild-to-moderate in severity. Few patients (≤ 6 in each treatment group) experienced serious adverse events or discontinued treatment due to a TEAE. As already described¹³, there was one death (due to intentional injury) in the dulaglutide 0.75 mg group that was not considered related to the study drug. TEAEs reported by $\geq 5\%$ of patients were hyperlipidemia, diarrhea, nasopharyngitis, lipase increased, dyslipidemia, decreased appetite, abdominal distension, nausea and vomiting (Table 2). Drug-related TEAEs were more common in both of the dulaglutide groups versus the glimepiride group (Table 2), mainly due to a higher incidence of TEAEs in the gastrointestinal system organ class (most frequently reported were: diarrhea, abdominal distension, nausea and vomiting). The incidence of gastrointestinal TEAEs was highest during the initial 2 weeks of treatment with dulaglutide (approximately 20%), but thereafter decreased rapidly ($< 5\%$ between weeks 2 and 4; Figure 7).

The incidence of all forms of hypoglycemia and the overall rate of hypoglycemia were lower in both of the dulaglutide groups versus the glimepiride group (Table 3). There were no events of severe hypoglycemia reported.

Throughout the 26-week treatment period, bodyweight decreased from baseline in both of the dulaglutide groups, but increased from baseline in the glimepiride group (Figure 8). The week 26 LSM changes from baseline in bodyweight were: dulaglutide 1.5 mg, -1.5 kg (SE 0.2 kg); dulaglutide 0.75 mg, -1.0 kg (SE 0.2 kg); glimepiride, 0.9 kg (SE 0.2 kg).

Cardiovascular safety findings were generally similar between the treatment groups. The mean decrease from baseline in systolic blood pressure was numerically more pronounced in the dulaglutide groups (dulaglutide 1.5 mg, -1.55 mmHg; dulaglutide 0.75 mg, -1.50 mmHg) versus the glimepiride group (-0.16 mmHg). Likewise, the mean increase from baseline in pulse rate was numerically more pronounced in both of the dulaglutide treatment groups (dulaglutide 1.5 mg, 3.99 b.p.m.; dulaglutide 0.75 mg, 2.66 b.p.m.) versus the glimepiride group (0.42 b.p.m.). The pulse rate interval increased from baseline in both of the dulaglutide groups (dulaglutide 1.5 mg, 3.09 s; dulaglutide 0.75 mg, 3.93 s), and decreased from baseline in the glimepiride group (-0.14 s). One patient treated with dulaglutide 0.75 mg reported a transient ischemic attack, which was confirmed as being a cardiovascular adjudicated event. This event was not fatal.

No patients experienced adjudicated acute or chronic pancreatitis. The increases from baseline in total amylase, pancreatic amylase and lipase concentrations were numerically greater in both of the dulaglutide groups versus the glimepiride group (Table S3).

No patients experienced thyroid neoplasm, medullary thyroid carcinoma or C-cell hyperplasia. Changes from baseline in calcitonin were minimal in all three groups (Table S4).

During the study, a relatively low proportion (19/370; 5.0%) of patients had treatment-emergent dulaglutide ADAs. Except for two patients, all ADAs developed after baseline (the highest titer reported was 1:32).

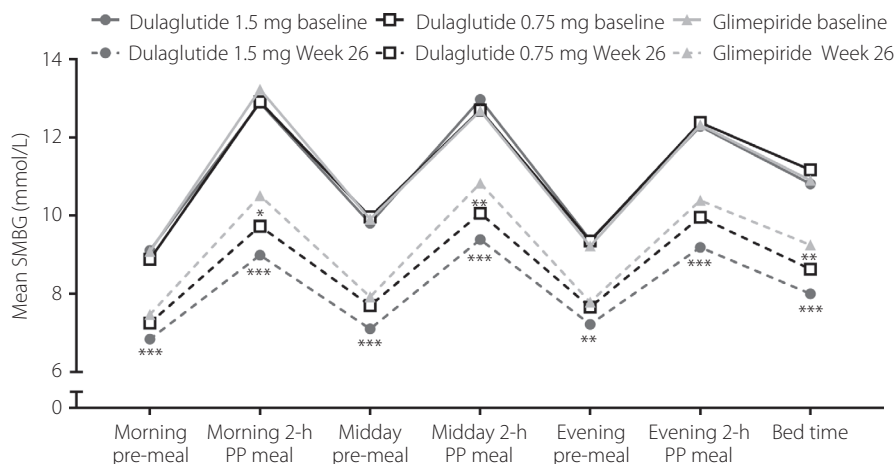


Figure 6 | Seven-point self-monitored blood glucose (SMBG) profiles by time of assessment at baseline and week 26 in Chinese patients with type 2 diabetes who were treated with dulaglutide 1.5 mg, dulaglutide 0.75 mg or glimepiride. * $P < 0.05$ versus glimepiride; ** $P < 0.001$ versus glimepiride; *** $P < 0.001$ versus glimepiride.

Table 2 | Safety overview

n (%)	Dulaglutide 1.5 mg (n = 189)	Dulaglutide 0.75 mg (n = 194)	Glimepiride (n = 187)	Total (n = 570)
Patients with ≥ 1 TEAE	129 (68.3)	112 (57.7)	110 (58.8)	351 (61.6)
Patients with ≥ 1 SAE	6 (3.2)	3 (1.5)	3 (1.6)	12 (2.1)
Patients who discontinued treatment due to a TEAE	6 (3.2)	4 (2.1)	3 (1.6)	13 (2.3)
Patients who died on therapy	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Patients with ≥ 1 drug-related TEAE	72 (38.1)	43 (22.2)	20 (10.7)	135 (23.7)
Most common TEAEs [†]				
Hyperlipidemia [‡]	27 (14.3)	30 (15.5)	41 (21.9)	98 (17.2)
Diarrhea	35 (18.5)	18 (9.3)	7 (3.7)	60 (10.5)
Nasopharyngitis	11 (5.8)	11 (5.7)	10 (5.3)	32 (5.6)
Lipase increased	14 (7.4)	12 (6.2)	5 (2.7)	31 (5.4)
Dyslipidemia	8 (4.2)	9 (4.6)	11 (5.9)	28 (4.9)
Decreased appetite	13 (6.9)	11 (5.7)	1 (0.5)	25 (4.4)
Abdominal distension	15 (7.9)	5 (2.6)	4 (2.1)	24 (4.2)
Nausea	18 (9.5)	5 (2.6)	1 (0.5)	24 (4.2)
Vomiting	12 (6.3)	1 (0.5)	0 (0.0)	13 (2.3)

[†]Reported by $\geq 5\%$ of patients in any treatment group. [‡]Lipid profile was measured at randomization (visit 3) for the first time with the treatment-emergent adverse event (TEAE) collected from the lead-in phase, leading to the high incidence of hyperlipidemia. SAE, serious adverse event.

Few patients experienced drug-related hypersensitivity reactions (dulaglutide 1.5 mg, $n = 1$; dulaglutide 0.75 mg, $n = 2$ [including 1 event of mild urticaria]; glimepiride, $n = 1$), and none of the patients who did experience drug-related hypersensitivity reactions developed treatment-emergent ADAs.

DISCUSSION

These post-hoc analyses are the first to examine the efficacy and safety of dulaglutide monotherapy in Chinese patients with type 2 diabetes who had inadequate

glycemic control and were either OAM-naïve or receiving OAM monotherapy. Notably, we found both doses of dulaglutide studied (1.5 and 0.75 mg) were both non-inferior and superior to glimepiride in providing glycemic control after 26 weeks of treatment. Improvements in secondary efficacy outcomes measures (percentage of patients who attained HbA1c targets, change in FBG, 7-point SMBG profile, insulin sensitivity and β -cell function) were also more pronounced (in most cases significantly) with dulaglutide. These improvements in efficacy

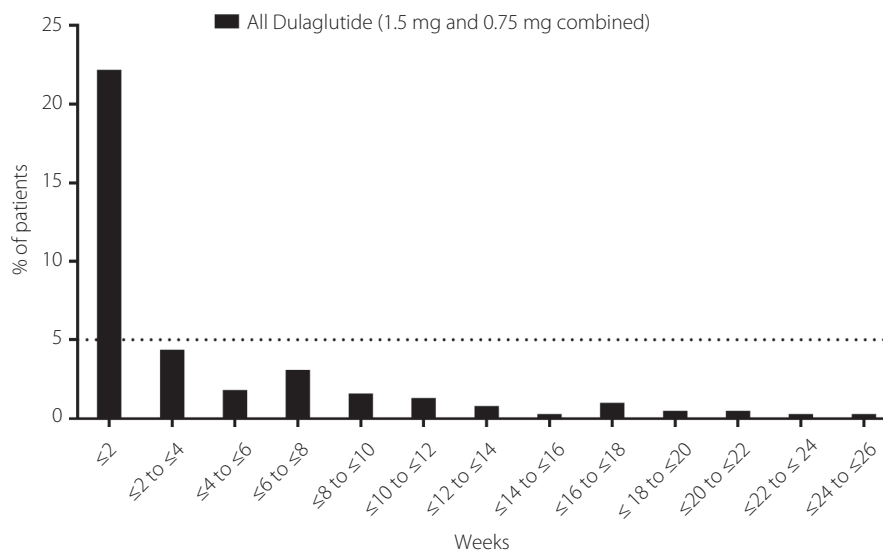


Figure 7 | Incidence of gastrointestinal treatment-emergent adverse events (per system organ class) over time in Chinese patients with type 2 diabetes who were treated with dulaglutide (1.5 and 0.75 mg combined).

Table 3 | Hypoglycemia overview

	Dulaglutide 1.5 mg (n = 189)	Dulaglutide 0.75 mg (n = 194)	Glimepiride (n = 187)	Total (n = 570)
All hypoglycemic episodes				
No. episodes	14	10	76	100
Incidence, n (%)	12 (6.3)	8 (4.1)	33 (17.6)	53 (9.3)
Rate, mean ± SD (events/patient/year)	0.14 ± 0.59	0.09 ± 0.51	1.39 ± 8.03	
Severe hypoglycemia [†]				
No. episodes	0	0	0	0
Incidence, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nocturnal hypoglycemia [‡]				
No. episodes	1	1	9	11
Incidence, n (%)	1 (0.5)	1 (0.5)	5 (2.7)	7 (1.2)
Documented symptomatic hypoglycemia [§]				
No. episodes	1	2	32	35
Incidence, n (%)	1 (0.5)	2 (1.0)	14 (7.5)	17 (3.0)
Asymptomatic hypoglycemia				
No. episodes	6	3	29	38
Incidence, n (%)	5 (2.6)	2 (1.0)	22 (11.8)	29 (5.1)
Probable hypoglycemia ^{**}				
Number of episodes	7	5	15	27
Incidence, n (%)	7 (3.7)	4 (2.1)	10 (5.3)	21 (3.7)

[†]Defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. These episodes might be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements might not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration. [‡]Defined as any hypoglycemic event that occurred between bedtime and waking. [§]Defined as any time a patient felt that he/she was experiencing symptoms and/or signs associated with hypoglycemia and had a plasma glucose concentration ≤ 3.9 mmol/L. ^{||}Defined as an event not accompanied by typical symptoms of hypoglycemia, but with a measured plasma glucose concentration of ≤ 3.9 mmol/L. ^{**}Defined as an event during which symptoms of hypoglycemia were not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L). SD, standard deviation.

with dulaglutide coincided with decreased hypoglycemia and weight loss versus glimepiride, and, overall, no new safety concerns. Taken together, these findings show that

dulaglutide monotherapy is an efficacious treatment for Chinese patients with type 2 diabetes and has a favorable safety profile.

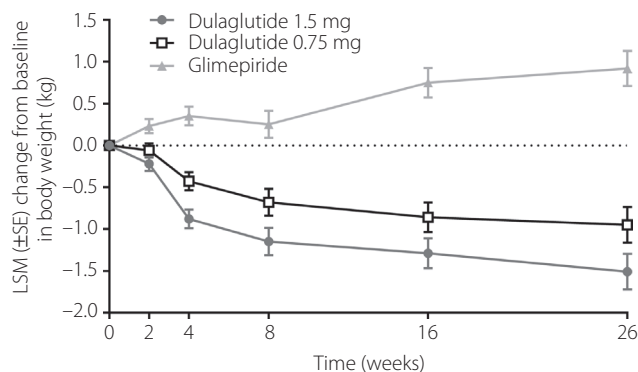


Figure 8 | Change in bodyweight from baseline over time in Chinese patients with type 2 diabetes who were treated with dulaglutide 1.5 mg, dulaglutide 0.75 mg or glimepiride. LSM, least-squares mean; SE, standard error.

Our findings from the present post-hoc analysis that dulaglutide monotherapy (both 1.5 mg and 0.75 mg doses) in Chinese patients with type 2 diabetes resulted in significantly more pronounced decreases in HbA1c from baseline versus glimepiride are consistent with the previously reported overall findings of this study¹³. Also similar to the overall study findings¹³, the magnitude of decrease in HbA1c from baseline with dulaglutide in Chinese patients was more pronounced than observed with dulaglutide monotherapy in the AWARD-3 study⁷, which included predominantly Caucasian participants. As previously noted and discussed in further detail¹³, differences in patient factors likely underlie this difference in the magnitude of HbA1c decrease, including body mass index, background therapy and baseline HbA1c. Of interest, a closer examination of the overall study findings suggests that dulaglutide shows low ethnic sensitivity among East Asian patients who have type 2 diabetes. This is evidenced by a similar magnitude of decrease from baseline to week 26 in HbA1c with dulaglutide monotherapy (1.5 and 0.75 mg) in patients from China (−1.46 and −1.25%), the Taiwan region (−1.53 and −1.22%) and Korea (−1.57 and −0.99%; data from Taiwan region and Korea; Eli Lilly and Company, unpubl. data).

Also consistent with the overall study findings¹³, we found that Chinese patients treated with dulaglutide, in particular dulaglutide 1.5 mg, experienced significantly more pronounced improvements in FBG, 7-point SMBG profiles (including post-prandial glucose excursions), insulin sensitivity and β -cell function, and more commonly attained HbA1c targets than patients treated with glimepiride.

There were no unexpected safety findings in our post-hoc analyses of Chinese patients with type 2 diabetes. Of note, dulaglutide treatment was associated with decreased hypoglycemia versus glimepiride, and a decrease in bodyweight loss. These findings are consistent with those of the overall study¹³ and a previous study that compared another glucagon-like peptide-1 receptor agonist, liraglutide, with glimepiride¹⁵. Other safety findings, including a transient occurrence at the start of treatment of gastrointestinal drug-related TEAEs, elevated

pancreatic enzymes (with no adjudicated instances of acute or chronic pancreatitis), and few treatment-emergent dulaglutide ADAs, are also in keeping with the overall study findings¹³ and other dulaglutide studies^{4–10}.

The limitations of the study underlying this post-hoc analysis have been described previously¹³.

In conclusion, we found that dulaglutide 1.5 or 0.75 mg once-weekly monotherapy provided superior glycemic control versus glimepiride in Chinese patients with type 2 diabetes. Other efficacy findings also favored dulaglutide, including changes in FBG and SMBG, and the proportion of patients who attained HbA1c targets. Importantly, the safety profile of dulaglutide in this patient population was consistent with that expected for a glucagon-like peptide-1 receptor agonist. Taken together, these findings show that once-weekly dulaglutide monotherapy has a favorable risk-to-benefit ratio and, therefore, might be an effective therapeutic option for Chinese patients who have early-stage type 2 diabetes.

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DISCLOSURE

LYD and FW are employees of Lilly Suzhou Pharmaceutical Co. Ltd. LXS, XML, YQS, QML, JHM, YBL and LLC declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Summary of change in 7-point self-monitored blood glucose concentrations from baseline to week 26.

Table S2 | Change in β -cell function and insulin sensitivity from baseline to week 26.

Table S3 | Summary of pancreatic enzyme concentrations at baseline and week 26.

Table S4 | Summary of calcitonin concentrations at baseline and week 26.