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ORIGINAL RESEARCH

Efficacy and Safety of Dulaglutide Monotherapy Compared to Glimepiride in Oral Antihyperglycemic Medication-Naïve Chinese patients with Type 2 Diabetes: A Post Hoc Analysis of AWARD-CHN1

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ABSTRACT

Introduction: Glucagon-like peptide (GLP)-1 receptor agonists are glucose-lowering agents associated with weight loss, cardiovascular benefits, and low hypoglycemic risk and are recommended by recent guidelines as first-line therapy for some patients with type 2 diabetes (T2D). This post hoc analysis of the AWARD-CHN1 study compared the efficacy and safety of once-weekly dulaglutide with glimepiride in oral antihyperglycemic medication (OAM)-naïve Chinese patients with T2D.

Methods: AWARD-CHN1 was a phase 3, double-blind study with 737 patients randomized 1:1:1 to once-weekly dulaglutide (1.5 or 0.75 mg) or glimepiride (1–3 mg/day). This is a post hoc analysis of AWARD-CHN1 based on mixed-model repeated measures using a modified intent-to-treat analysis set with only the OAM-naïve Chinese population.

Results: There were 264 OAM-naïve Chinese patients included in this analysis (dulaglutide 1.5 mg, $n = 87$; dulaglutide 0.75 mg, $n = 90$; glimepiride, $n = 87$). A greater glycated hemoglobin (HbA1c) reduction from baseline was observed with dulaglutide 1.5 mg and 0.75 mg compared to glimepiride (− 2.02% and − 1.84% vs − 1.37%, respectively; both $P < 0.001$). Significantly more patients in dulaglutide 1.5 mg and 0.75 mg groups achieved HbA1c targets < 7.0% compared to glimepiride (86.2% and 81.1% vs 65.5%; $P = 0.002$ and $P = 0.026$, respectively). Beta cell function was significantly increased for dulaglutide groups compared to glimepiride. Mean body weight was significantly reduced for dulaglutide 1.5 mg and 0.75 mg compared to glimepiride (− 1.40 kg and − 0.96 kg vs + 0.73 kg, respectively; both

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$P < 0.001$). Through 26 weeks, 7.9%, 4.2%, and 18.2% of patients reported hypoglycemia, and 40.4%, 23.2%, and 8.0% of patients reported at least one gastrointestinal treatment emergent adverse event, in dulaglutide 1.5 mg, 0.75 mg, and glimepiride groups, respectively.

Conclusions: In this post hoc analysis, dulaglutide was effective in reducing both HbA1c and weight with favorable tolerability and safety profile, which is consistent with results seen in larger international dulaglutide monotherapy studies.

Trial Registration: ClinicalTrials.gov NCT01644500.

Keywords: China; Dulaglutide; Glimepiride; Type 2 diabetes

Key Summary Points

Why carry out this study?

Current study is a post hoc analysis of AWARD-CHN1 and evaluates efficacy and safety of once-weekly monotherapy of dulaglutide (1.5 mg and 0.75 mg) in OAM-naïve Chinese patients with type 2 diabetes (T2D) in comparison to glimepiride.

What was learned from the study?

Both the dulaglutide doses (1.5 mg and 0.75 mg) demonstrated significant reduction in HbA1c levels, with higher proportions of patients achieving HbA1c < 7% and ≤ 6.5% and greater reduction in FBG and SMBG levels, and significantly improved beta cell function, with a substantially lower risk of hypoglycemia, compared with glimepiride.

The overall findings from the current post hoc analysis demonstrate the potential for once-weekly dulaglutide monotherapy as a treatment for OAM-naïve Chinese patients with T2D, consistent with larger, international dulaglutide monotherapy studies.

INTRODUCTION

China currently has the world's largest population of patients with diabetes, and prevalence of the disease has increased from 0.67% in 1980 to an estimated 10.9% in 2013. With China's estimated 35.7% prevalence of prediabetes in 2013, treatment and prevention of type 2 diabetes (T2D) is a major public health issue [1, 2]. T2D is a progressive disease characterized by insulin resistance and impaired beta cell function, with beta cell failure caused by the increasing demands associated with insulin resistance [3]. According to data in the UK Prospective Diabetes Study [4], and from a study on preservation of beta cell function [5], about 50–80% of beta cell function may have decreased by the time diabetes is diagnosed. Treatments targeting these aspects are therefore essential to manage T2D. Glucagon-like peptide (GLP)-1 receptor agonists which mimic the gluco-regulatory actions of GLP-1 and resist dipeptidyl peptidase (DPP)-4 degradation have demonstrated efficacy to reduce glycated hemoglobin (HbA1c) with unique pharmacological effects that include delayed gastric emptying, diminished appetite, and glucose-dependent enhanced insulin secretion. GLP-1 receptor agonists can also improve beta cell function, as assessed by homeostatic model assessment (HOMA)-B analysis and proinsulin-to-insulin ratio, and markedly improve first- and second-phase insulin responses, and are able to restore beta cell sensitivity to glucose [3]. Additionally, GLP-1 receptor agonists are effective glucose-lowering agents associated with weight loss, cardiovascular benefits, and low risk of hypoglycemia, providing advantages over sulfonylureas, which are associated with hypoglycemia and weight gain, but are still widely used across East Asia [6–8].

Dulaglutide is a long-acting, once-weekly human GLP-1 receptor agonist approved to treat T2D. The dulaglutide molecule consists of two identical disulfide-linked chains. Each of these chains contains an N-terminal GLP-1 analogue sequence covalently bonded to a modified human immunoglobulin G4 Fc fragment with a small peptide. Compared to native human GLP-1, the GLP-1 analogue portion of dulaglutide is 90% homologous. The analogue portion also contains amino acid substitutions designed to improve the dulaglutide clinical profile, so that it resists degradation from DPP-4, is more soluble, and is less likely to trigger an immune response. Likewise, dulaglutide delays absorption and decreases renal clearance, hence making dulaglutide a more soluble formulation with a prolonged half-life of approximately 5 days and convenient for once-weekly subcutaneous dose administration [9–11].

In phase 3 studies, dulaglutide has demonstrated significant HbA1c reductions with both fasting and postprandial glucose improvements and weight loss [12–15]. The AWARD-CHN1 trial was the first to evaluate the efficacy and safety of dulaglutide (0.75 and 1.5 mg) to treat T2D in East-Asian patients with inadequate glycemic control who were either oral antihyperglycemic medication (OAM)-naïve or on OAM monotherapy. This 26-week, multinational, double-blind, randomized, parallel-arm, phase 3 trial randomized patients with T2D 1:1:1 to dulaglutide 1.5 mg, 0.75 mg, or glimepiride (1–3 mg/day), and demonstrated that both doses of dulaglutide had improved glycemic control and a higher number of patients who achieved target HbA1c levels compared to those receiving glimepiride.

Given the favorable risk–benefit profile for GLP-1 receptor agonists, it has been given increasing priority in diabetes treatment recommendations, with some guidelines suggesting it should be first-line therapy [16]. This post hoc analysis of AWARD-CHN1 investigates the safety and efficacy of dulaglutide versus glimepiride in OAM-naïve Chinese patients.

METHODS

Ethics

The AWARD-CHN1 study (ClinicalTrials.gov NCT01644500) protocol was reviewed and approved by the institutional ethics committee at each study center and was conducted in accordance with the principles of the Declaration of Helsinki [17], Good Clinical Practice guidelines, and applicable laws and regulations. Written informed consent was obtained from each patient before participation.

Study Design and Patients

The AWARD-CHN1 study was a randomized, double-blind, parallel-arm, active comparator, phase 3 study conducted over 26 weeks in East-Asian countries. The study design and eligibility criteria have been described previously [15]. Patients with T2D aged 18 years or more who were OAM-naïve (with HbA1c $\geq$ 7.0% and $\leq$ 10.5% at screening) or discontinued from OAM monotherapy for at least 3 months before screening (with HbA1c $\geq$ 6.5% and $\leq$ 10.0% at screening) were included. Key exclusion criteria were diagnosis of type 1 diabetes, prior treatment with GLP-1 receptor agonists or GLP-1 analogues, ongoing treatment with DPP-4 inhibitors or thiazolidinediones, or current or prior (within 3 months before visit 1) chronic insulin treatment.

This post hoc analysis of AWARD-CHN1 only included Chinese OAM-naïve patients.

Study Treatment

Eligible patients were randomly assigned 1:1:1 according to a computer-generated random sequence using an interactive voice response system to receive once-weekly dulaglutide (1.5 mg), once-weekly dulaglutide (0.75 mg), or glimepiride (1–3 mg/day). The randomization was stratified by baseline HbA1c (visit 3).

Assessments

The primary efficacy endpoint analyzed in this post hoc analysis was a comparison of the change in HbA1c from baseline at week 26 among the two dulaglutide and the glimepiride treatment groups. Other efficacy measures analyzed were the proportion of patients attaining HbA1c levels < 7% or $\leq$ 6.5%, changes in fasting blood glucose (FBG) profile, 7-point self-monitored blood glucose (SMBG) profile, blood glucose excursions, and calculations of the updated version of homeostasis model assessment (HOMA2) (computed using fasting blood glucose, insulin, and C-peptide concentrations) of beta cell function (HOMA2-%B). Safety and tolerability were evaluated throughout by the assessments of weight change, hypoglycemic episodes, and treatment-emergent adverse events (TEAEs).

Statistical Analysis

The primary efficacy analysis, change in HbA1c from baseline at 26 weeks, was conducted on a mixed-model repeat measurement analysis using the modified intention-to-treat analysis set, which included all randomized Chinese OAM-naïve patients who had a baseline HbA1c measurement and at least one post-baseline HbA1c measurement and received at least one dose of study drug. The HbA1c test results for visit 3 were used as the baseline HbA1c concentration for the purpose of statistical analyses. For secondary efficacy analysis, between-treatment differences (both dulaglutide doses versus glimepiride) in the percentages of patients with HbA1c < 7.0% or ≤ 6.5% at 26 weeks were analyzed using Fisher's exact test. Safety analyses were conducted on an as-treated analysis set that included Chinese OAM-naïve patients who received at least one dose of study drug and were analyzed according to the treatment they received, regardless of their planned treatment. All tests of the treatment effect were conducted at a one-sided alpha level of 0.025, assuming no true difference between treatments. Two-sided 95% confidence intervals (CIs) were included in the presentation of the results.

RESULTS

A total of 264 patients were included in this post hoc analysis (dulaglutide 1.5 mg = 87; dulaglutide 0.75 mg = 90; glimepiride = 87). Demographics and baseline characteristics of OAM-naïve patients are described in Table 1. A total of 101 (38.3%) patients were female, the mean (SD) HbA1c was 8.13% (1.03), and the mean duration of T2D was 1.55 years. Baseline characteristics were similar in the three treatment groups.

Table 1 Demographic and baseline characteristics of OAM-naïve Chinese patients

Variables	DU 1.5 mg (*N* = 87)	DU 0.75 mg (*N* = 90)	Glimepiride (*N* = 87)
Sex female, *n* (%)	31 (35.6)	32 (35.6)	38 (43.7)
Age, years	49.6 (11.1)	52.4 (8.9)	50.9 (9.7)
BMI, kg/m^2	25.6 (3.3)	25.9 (3.3)	25.3 (2.8)
Body weight, kg	70.3 (10.5)	71.9 (11.5)	69.1 (10.1)
HbA1c, %	8.11 (1.03)	8.21 (1.05)	8.07 (1.01)
Duration of diabetes, years	1.5 (2.2)	1.8 (2.5)	1.4 (2.3)

Unless indicated otherwise, data are presented as the mean (± SD)

BMI body mass index, *DU* dulaglutide, *HbA1c* glycated hemoglobin A1c, *kg* kilogram, *kg/m*^{2} kilograms per square meter, *N* total number of patients in specified treatment, *n* number of patients in specified category, *OAM* oral antidiabetic medication, *SD* standard deviation

At week 26, the least-squares mean (standard error) (LSM [SE]) change from baseline in HbA1c was greater in the dulaglutide 1.5 mg (– 2.02% [0.09]) and dulaglutide 0.75 mg (– 1.84% [0.09]) treatment groups than in the glimepiride (– 1.37% [0.09]) treatment group. The LSM for the differences between each dose of dulaglutide versus glimepiride was – 0.65% (95% CI – 0.91, – 0.39) for dulaglutide 1.5 mg and – 0.47% (95% CI – 0.73, – 0.21) for dulaglutide 0.75 mg at week 26, $P < 0.001$ for both comparisons (Fig. 1). Overall, the HbA1c reduction was significantly greater with both doses of dulaglutide compared to glimepiride. Figure 2 shows LSM (SE) change in HbA1c by visit from baseline to week 26 in all treatment groups.

At week 26, significantly greater proportions of patients achieved a decrease in HbA1c level to < 7.0% in the dulaglutide 1.5 mg and 0.75 mg groups compared with the glimepiride group (86.2% vs 65.5%, $P = 0.002$ for dulaglutide 1.5 mg and 81.1% vs 65.5%, $P = 0.026$ for dulaglutide 0.75 mg). Similarly, a significantly greater proportion of patients achieved a

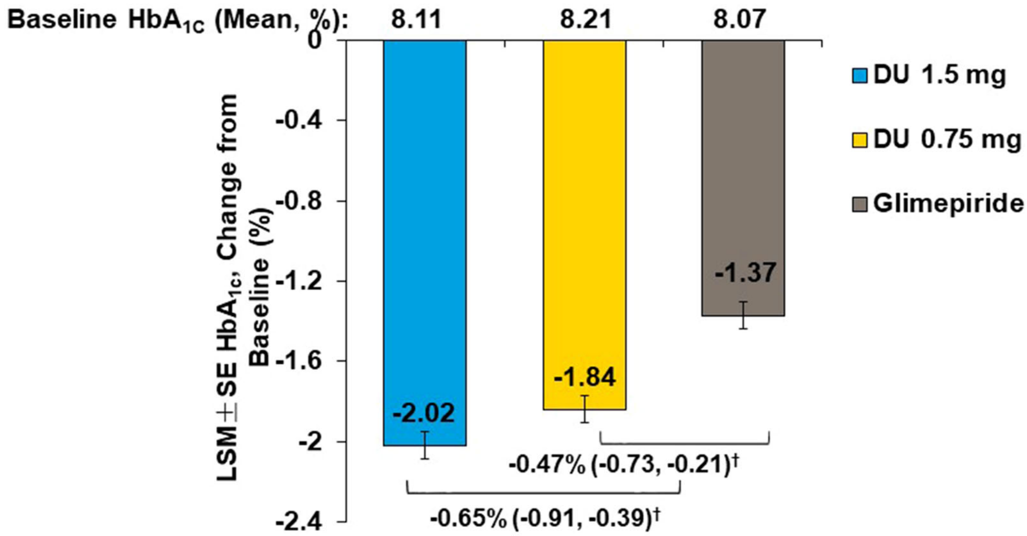

Fig. 1 Changes from baseline in HbA1c at week 26 in OAM-naïve Chinese patients using mITT population. †$P < 0.001$, DU 1.5 mg vs glimepiride and DU 0.75 mg vs glimepiride, an LSM difference (95% CI) of dulaglutide with glimepiride. LSM are based on mixed-model repeated measures analysis. CI confidence interval, DU dulaglutide, HbA1c glycated hemoglobin A1c, LSM least-squares mean, mITT modified intention-to-treat, OAM oral antidiabetic medication, SE standard error

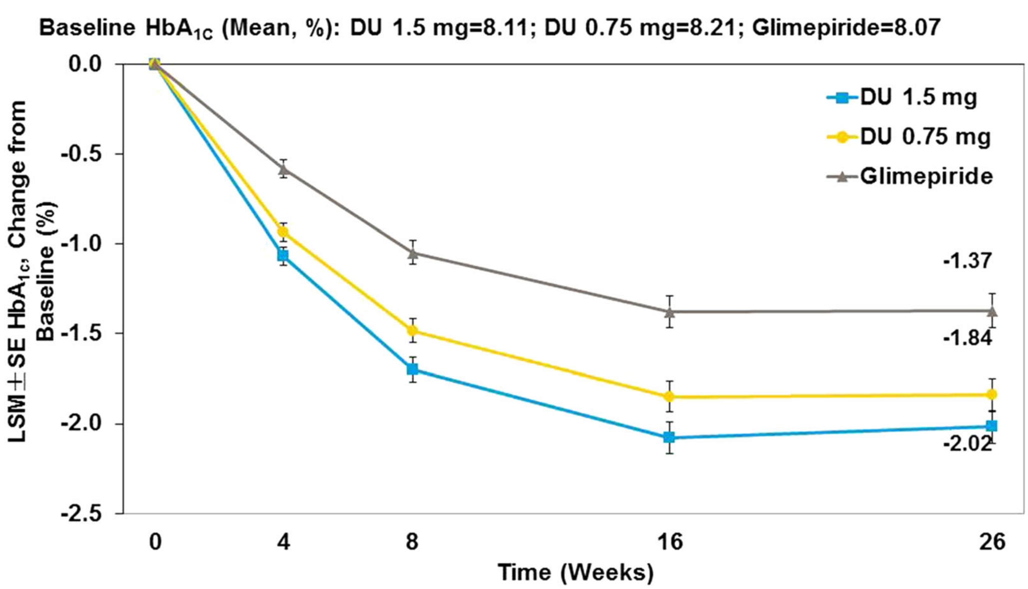

Fig. 2 Changes in HbA1c from baseline over time to week 26 in OAM-naïve Chinese patients using mITT population. LSM are based on mixed-model repeated measures analysis. DU dulaglutide, HbA1c glycated hemoglobin A1c, LSM least-squares mean, mITT modified intention-to-treat, OAM oral antidiabetic medication, SE standard error

reduction in HbA1c level to ≤ 6.5% in the dulaglutide 1.5 mg compared with the glimepiride group (71.3% vs 51.7%; $P = 0.012$). The proportion of patients achieving an HbA1c level of ≤ 6.5% at week 26 was numerically greater in the dulaglutide 0.75 mg group than the glimepiride group (63.3% vs 51.7%; $P = 0.130$) (Fig. 3).

The LSM (SE) change in FBG from baseline to week 26 was significantly greater ($P < 0.01$) in the dulaglutide 1.5 mg group compared with the glimepiride group (− 2.32 mmol/L [0.17] vs − 1.66 mmol/L [0.17]; $P = 0.007$]). No statistically significant difference in the change from baseline in FBG at week 26 was observed between the dulaglutide 0.75 mg and glimepiride groups (− 1.94 mmol/L [0.17] vs − 1.66 mmol/L [0.17]; $P = 0.242$) (Fig. 4).

At each time point, the mean blood glucose values on the 7-point SMBG profile at week 26 were lower compared with baseline in all treatment groups. At week 26, a greater reduction in the 7-point SMBG profile was observed for dulaglutide 1.5 mg compared with glimepiride at all time points. The reductions in 7-point SMBG were also greater with dulaglutide 0.75 mg compared to glimepiride at morning pre-meal, morning 2-h postprandial meal, midday 2-h postprandial meal, evening 2-h postprandial meal, and at bedtime assessments (Fig. 5).

Over the 26-week treatment period, patients in both dulaglutide groups experienced weight loss. Conversely, patients in the glimepiride group gained weight. At week 26, the LSM (SE) change from baseline in body weight for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glimepiride was − 1.40 (0.318) kg, − 0.96 (0.312) kg, and 0.73 (0.311) kg, respectively (Fig. 6).

At week 26, significant increases in insulin- and C-peptide-based HOMA2 for beta cell function were observed in comparisons between both dulaglutide groups with glimepiride ($P < 0.001$ for dulaglutide 1.5 mg vs glimepiride and $P < 0.05$ for dulaglutide 0.75 mg vs glimepiride) (Fig. 7).

A total of 65 patients experienced at least one gastrointestinal (GI) TEAE during the 26-week study period (36 [40.4%] in dulaglutide 1.5 mg, 22 [23.2%] in dulaglutide 0.75 mg, and 7 [8.0%] in the glimepiride group). The total, documented, and nocturnal hypoglycemia rates (per year) were greater in the glimepiride group compared with both dulaglutide groups (Fig. 8). No episodes of severe hypoglycemia were observed in any group during the 26-week treatment period. The most frequently reported GI TEAEs included diarrhea, nausea, and abdominal distension, with a higher incidence reported in the dulaglutide groups compared with glimepiride (Table 2).

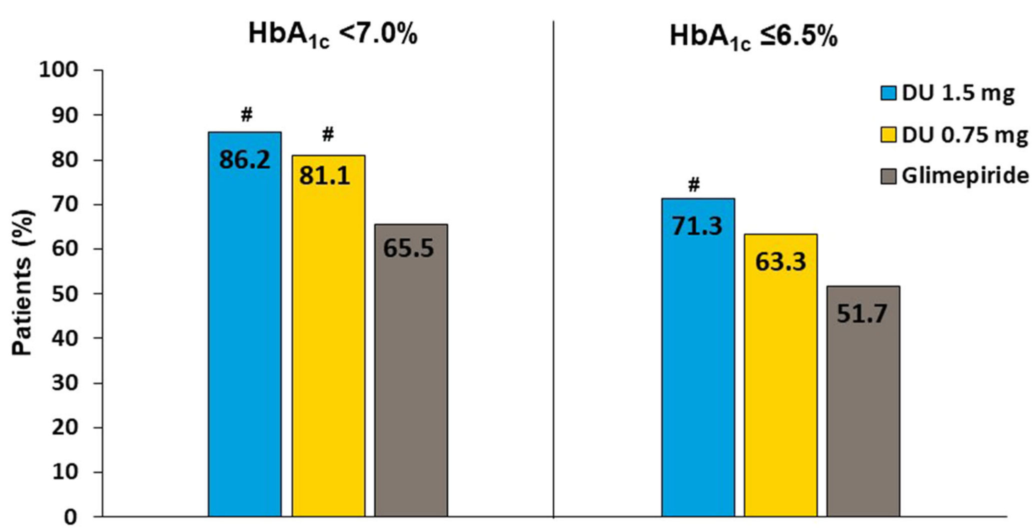

Fig. 3 Percentage of OAM-naïve Chinese patients achieving HbA1c targets at week 26. *P* value is based on Fisher's exact test. #$P < 0.05$ for DU 1.5 mg vs glimepiride and DU 0.75 mg vs glimepiride. DU dulaglutide, HbA1c glycated hemoglobin A1c, OAM oral antidiabetic medication

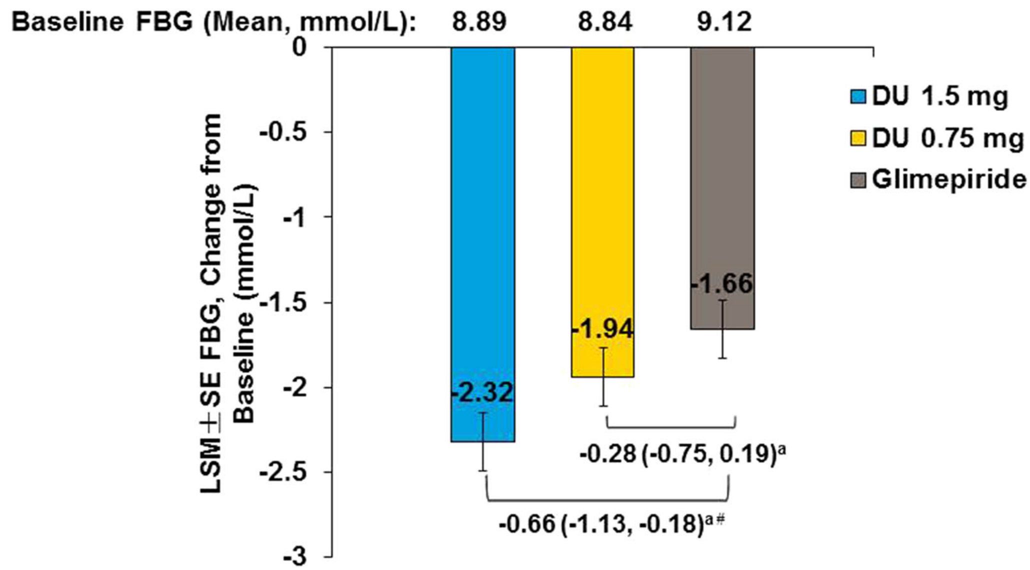

Fig. 4 Change in fasting blood glucose from baseline to week 26 in OAM-naïve Chinese patients (mITT population). [a]LSM difference (95% CI) of dulaglutide with glimepiride. LSM are based on mixed-model repeated measures analysis. $^{\#}P < 0.01$ dulaglutide 1.5 mg vs glimepiride. CI confidence interval, DU dulaglutide, FBG fasting blood glucose, LSM least-squares mean, mITT modified intention-to-treat, OAM oral antidiabetic medication, SE standard error

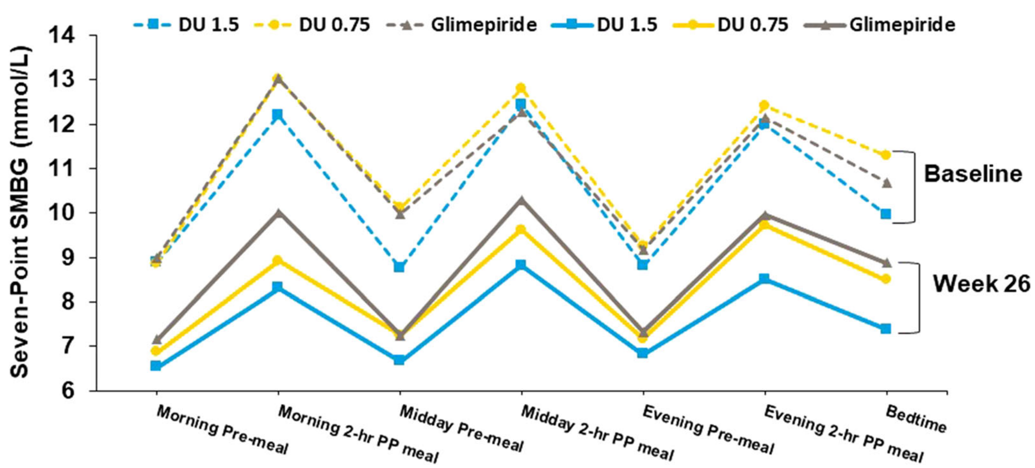

Fig. 5 Seven-point self-monitored blood glucose (SMBG) profiles by time of day in OAM-naïve Chinese patients. DU dulaglutide, hr hour, OAM oral antidiabetic medication, SMBG self-monitored blood glucose, PP post-prandial

DISCUSSION

This post hoc analysis of the AWARD-CHN1 study is the first analysis designed to demonstrate the efficacy and safety of both doses of dulaglutide (1.5 mg and 0.75 mg) in OAM-naïve Chinese patients with T2D compared to glimepiride. The results demonstrated that both doses of dulaglutide resulted in greater reduction in HbA1c levels compared to glimepiride after 26 weeks of treatment. The improvements observed in other efficacy outcome measures (i.e., percentage of patients who attained HbA1c targets, and changes in FBG profile, 7-point

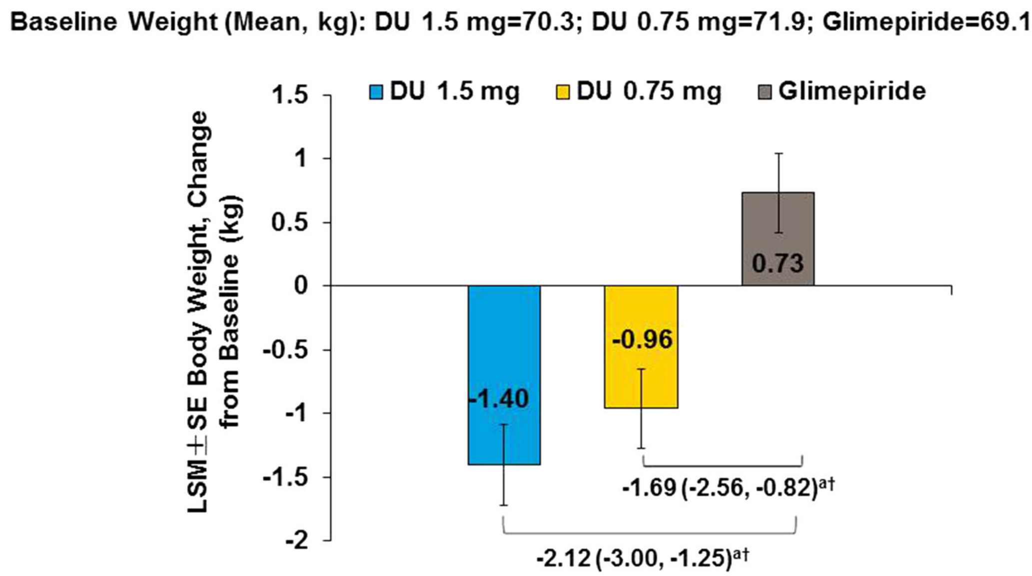

Fig. 6 Change in body weight from baseline to 26 weeks in Chinese patients with T2D who were OAM-naïve. [a]LSM difference (95% CI) of dulaglutide with glimepiride. LSM are based on mixed-model repeated measures analysis. $^{\dagger}P < 0.001$ dulaglutide vs glimepiride. CI confidence interval, DU dulaglutide, LSM least-squares mean, OAM oral antidiabetic medication, SE standard error, T2D type 2 diabetes

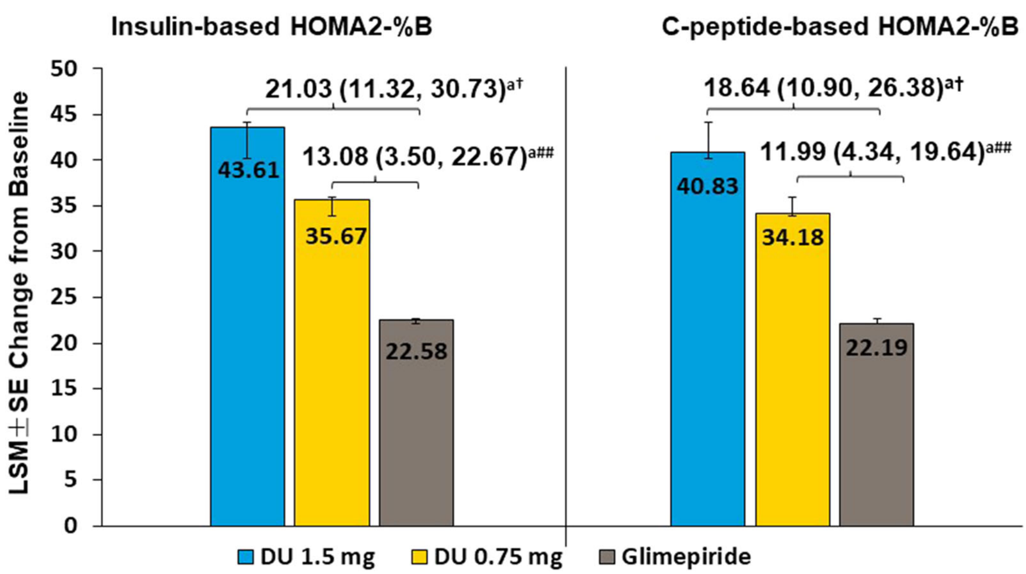

Fig. 7 Change in beta cell function from baseline to 26 weeks in Chinese patients with T2D who were OAM-naïve. [a]LSM difference (95% CI) of dulaglutide with glimepiride based on ANCOVA model. $^{\dagger}P < 0.001$ dulaglutide 1.5 mg vs glimepiride. $^{\#\#}P < 0.05$ dulaglutide 0.75 mg vs glimepiride in both insulin-based HOMA2-%B and C-peptide-based HOMA2-%B groups. CI confidence interval, HOMA2-%B updated homeostasis model assessment of beta cell function, LSM least-squares mean, *N* number of patients in the analyses population for the specified treatment group, OAM oral antidiabetic medication, SE standard error, T2D type 2 diabetes

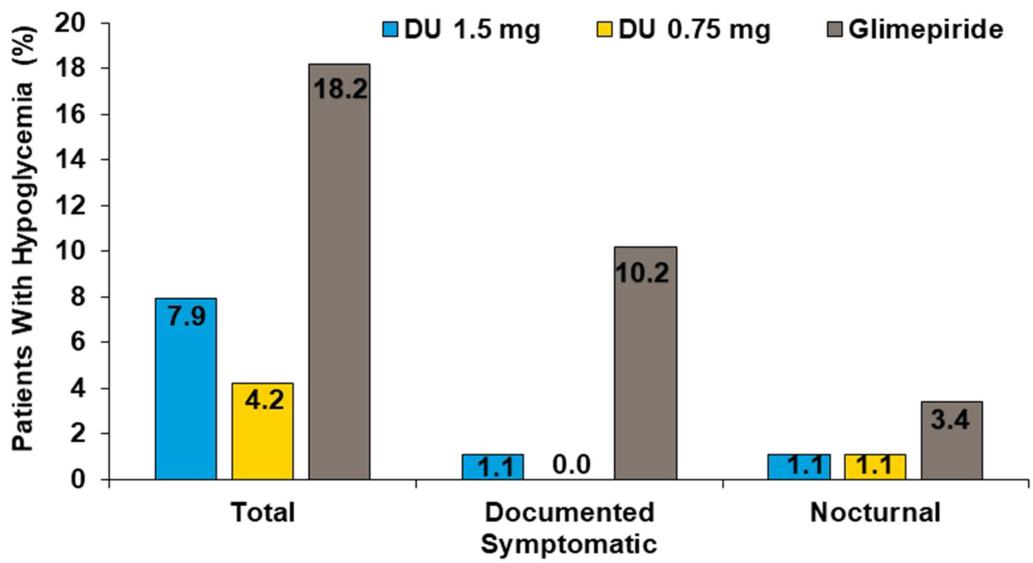

Fig. 8 Incidence of hypoglycemia up to 26 weeks in OAM-naïve Chinese patients. DU dulaglutide, OAM oral antidiabetic medication

SMBG profile, insulin sensitivity, and beta cell function) were also more pronounced after treatment with dulaglutide (both doses), which is consistent with the results of an overall study [15] and Chinese population [18].

Furthermore, in the overall population study [15], the Chinese subgroup [18], and the current OAM-naïve Chinese group, there were significantly more patients attaining HbA1c < 7.0% in the dulaglutide 1.5 mg group than in the glimepiride group (74.1% vs 57.4%, $P < 0.001$ for the overall population [15]; 71.7% vs 57.5%, $P = 0.005$ for Chinese subgroup [18]; 86.2% vs 65.5% $P = 0.002$ for patients who were OAM-naïve). Moreover, in this post hoc analysis, compared to glimepiride, a significantly greater proportion of patients treated with dulaglutide (1.5 mg and 0.75 mg) reached a target HbA1c of < 7.0%, with greater reductions in body weight and hypoglycemia at week 26. The finding of the present post hoc analysis is consistent with the post hoc analysis of AWARD-CHN1 and AWARD-CHN2 evaluating composite endpoints, in which 40–48% of patients on dulaglutide 1.5 mg, 30–39% of patients on dulaglutide 0.75 mg, and 15–20% of patients treated with active comparators (glimepiride/insulin glargine) reached a target HbA1c of < 7.0%, without weight gain or hypoglycemia at week 26 [19].

The significantly pronounced reduction in HbA1c observed in OAM-naïve patients in the current analysis with both dulaglutide doses was consistent with previously reported findings in a study of OAM-naïve patients [20] and other AWARD studies in which patients received OAM therapy [12–14]. Potential explanations for the greater reductions in HbA1c can be attributed to the lower body mass index (BMI) in the Asian population. BMI is highly correlated with insulin sensitivity [20–23], and an enhanced glycemic response in patients with lower baseline BMI can be certainly achieved [22]. Additionally, treatment with GLP-1 receptor agonists appears to be particularly more effective in Asian patients, who tend to have a pathophysiology of insulin secretion, since GLP-1 receptor agonists stimulate insulin secretion in a glucose-dependent manner and inhibit the release of glucagon [24, 25]. Another possible reason for greater HbA1c reduction is that the current analysis was conducted in patients with T2D who had no previous OAM therapy [26–28], which is a well-established baseline factor positively associated with favorable HbA1c response to antidiabetic drugs in clinical research [29].

Table 2 Gastrointestinal adverse events through 26 weeks in OAM-naïve Chinese patients

	DU 1.5 mg (N = 89)	DU 0.75 mg (N = 95)	Glimepiride (N = 88)
At least 1 GI TEAE, n (%)	36 (40.4)	22 (23.2)	7 (8.0)
Patients with ≥ 2% GI TEAE in any group, n (%)			
Diarrhea	20 (22.5)	10 (10.5)	3 (3.4)
Nausea	11 (12.4)	2 (2.1)	1 (1.1)
Abdominal distention	6 (6.7)	4 (4.2)	1 (1.1)
Vomiting	4 (4.5)	0 (0.0)	0 (0.0)
Constipation	3 (3.4)	1 (1.1)	0 (0.0)
Abdominal pain upper	3 (3.4)	2 (2.1)	0 (0.0)
Abdominal discomfort	2 (2.2)	2 (2.1)	3 (3.4)
Abdominal pain	2 (2.2)	0 (0.0)	0 (0.0)
Abdominal pain lower	2 (2.2)	1 (1.1)	0 (0.0)
GI disorder	3 (3.4)	1 (1.1)	0 (0.0)

Data presented are for safety population

DU dulaglutide, *GI* gastrointestinal, *N* total number of patients in specified treatment group, *n* number of patients in specified category, *OAM* oral antidiabetic medication, *TEAE* treatment-emergent adverse event

In the current analysis, treatment with dulaglutide was also associated with an increase in beta cell function as measured by HOMA2-%B. The increases of insulin-based and C-peptide-based HOMA2-%B were significantly greater for both dulaglutide 1.5 mg and 0.75 mg groups compared with the glimepiride group, and these findings were consistent with dulaglutide AWARD-3 study findings, in which changes with dulaglutide 1.5 mg and 0.75 mg were greater than those with metformin (both comparisons, $P \leq 0.001$) [14]. The improvements in HOMA2-%B in the current analysis provide great insight into the glucose-lowering mechanism of dulaglutide specifically related to enhanced pancreatic beta cell function. The duration of the study was relatively short considering the chronic nature of T2D, hence these HOMA2-%B results should be interpreted prudently. In the long run, the rise in HOMA2-%B may not translate into long-term improvement in beta cell function, and in fact may reflect a GLP-1 receptor agonist-mediated increase in insulin secretion [30].

The safety profile of dulaglutide in the present analysis of OAM-naïve patients is consistent with the overall study [15] and with previous data from AWARD studies [12–14] and other compounds in the GLP-1 receptor agonist class [31]. The most common drug-related adverse events reported in the present analysis were GI (e.g., diarrhea or nausea), which were transient and rarely led to treatment discontinuation. In this post hoc analysis, the incidence of hypoglycemia in both dulaglutide treatment groups was low and similar to previous AWARD studies [12, 13]. Additionally, the increase in pancreatic enzymes observed in the current analysis is consistent with results of earlier studies of dulaglutide [32] and the GLP-1 receptor agonist class of drugs [33]; no cases of pancreatitis were reported in any treatment groups in the current analysis. Both doses of dulaglutide showed significantly greater decreases in body weight compared with glimepiride at the end of the treatment period. The mechanisms of weight loss with GLP-1 receptor agonists are probably related to delayed gastric emptying and decreased food intake caused by increased satiety [34–36].

According to the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2019 diabetes management algorithm [37], GLP-1 receptor agonists are the second preferred choice of treatment as monotherapy in patients with HbA1c < 7.5% after metformin [37] and the preferred choice as dual therapy with metformin in patients with HbA1c ≥ 7.5%. However, in OAM-naïve patients, the AACE guideline suggests that patients with HbA1c > 7.5% and patients who are not on any antihyperglycemic drug treatment should start initially on metformin plus another agent [38]. In addition, according to the European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) 2019 guidelines, GLP-1 receptor agonists are recommended in patients with T2D and atherosclerotic cardiovascular disease or very high/high cardiovascular risk, whether they are treatment-naïve or already on metformin [16]. Also, according to the standards of care for T2D in China (2016), T2D blood glucose control strategy and treatment options and recommendations of International Diabetes Federation, the American Diabetes Association, and National Institute for Health and Clinical Excellence suggest initiating dual therapy with metformin and insulin secretagogues such as dulaglutide in patients with newly diagnosed T2D who have HbA1c $\geq$ 7% above their glycemic target. Thus, the current post hoc analysis suggests that dulaglutide in OAM-naïve patients reiterates the current guideline recommendations [39].

Limitations

The 26-week treatment period is relatively short for the assessment of glycemic control considering the chronic nature of T2D in OAM-naïve Chinese patients. Eventually, long-term studies are needed to evaluate the durability of weight and glycemic reductions made in this study. This post hoc analysis focused mainly on OAM-naïve patients; therefore, the applicability of this treatment in patients who are already on OAM treatment should be evaluated.

CONCLUSIONS

In this 26-week post hoc analysis, both dulaglutide doses demonstrated a significant reduction in HbA1c levels, higher proportion of patients achieved HbA1c $<$ 7% and $\leq$ 6.5%, greater reduction in FBG levels and SMBG levels, and significantly improved beta cell function with a substantially lower risk of hypoglycemia compared with glimepiride. These findings demonstrate the potential for once-weekly dulaglutide monotherapy as a treatment for OAM-naïve Chinese patients with T2D, consistent with larger, international dulaglutide monotherapy studies.

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Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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