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CLINICAL TRIAL

Achieving the composite end-point of glycated hemoglobin <7.0% without weight gain or hypoglycemia with once-weekly dulaglutide in Chinese patients with type 2 diabetes: A post-hoc analysis

Xinhua Xiao[1], Changjiang Wang[2], Xiaoyang Lai[3], Bin Zhang[4], Liqun Gu[4], Jianing Hou[5]*, Zhiguang Zhou[6]*

[1]Department of Endocrinology, Key Laboratory of Endocrinology, National Health Commission, Chinese Academy of Medical Science, Peking Union Medical College Hospital, Beijing, China, [2]The First Hospital of Anhui Medical University, Hefei, China, [3]The Second Affiliated Hospital of Nanchang University, Nanchang, China, [4]Lilly Suzhou Pharmaceutical Co. Ltd., Shanghai, China, [5]Clinical Research Physician, Diabetes Therapeutic Area, Eli Lilly and Company, Lilly Suzhou Pharmaceutical Co. Ltd, Shanghai, China, and [6]Institute of Metabolism and Endocrinology, Key Laboratory of Diabetes Immunology, Ministry of Education, National Clinical Research Center for Metabolic Diseases, The Second Xiangya Hospital, Central South University, Changsha, China

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***Correspondence**
Jianing Hou
Tel.: +86-21-2302-1068
Fax: +86-21-2302-0949
E-mail addresses:
hou_jia_ning@hotmail.com;
hou_jia_ning@lilly.com

Zhiguang Zhou
Tel.: +86-138-7310-4348
E-mail address:
zhouzg@hotmail.com

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ABSTRACT

Aims/Introduction: To assess the effect of dulaglutide (DU) 1.5/0.75 mg in comparison with glimepiride (GLIM) or insulin glargine (GLAR) on the composite end-point in Chinese type 2 diabetes patients.

Materials and Methods: Post-hoc analyses of two randomized phase III trials (NCT01644500 and NCT01648582) were carried out using Fisher's exact test. The primary composite end-point was the number of patients reaching glycated hemoglobin (HbA1c) <7.0%, without weight gain and hypoglycemia. Secondary composite end-points included the number of patients reaching HbA1c <7.0% without weight gain and HbA1c <7.0% without hypoglycemia.

Results: Data of 1,147 Chinese type 2 diabetes patients were analyzed (NCT01644500 = 556; NCT01648582 = 591). In each analyzed trial, 40–48% of patients received DU (1.5 mg), 30–39% of patients received DU (0.75 mg) and 15–20% of patients on active comparators (GLIM/GLAR) reached the primary composite end-point at week 26 ($P < 0.001$ for DU vs GLIM/GLAR). At 52 weeks, 26% of patients that received DU (1.5 mg), 23% of patients that received DU (0.75 mg) and 7% of patients that received GLAR attained the primary composite end-point ($P < 0.001$ for DU vs GLAR). A similar trend of results was found for secondary composite end-points.

Conclusions: Dulaglutide is found to be an effective therapeutic alternative for Chinese type 2 diabetes patients. Compared with GLIM/GLAR, significantly greater proportions of patients on DU attained the HbA1c target of <7.0% without weight gain or hypoglycemia.

INTRODUCTION

Globally, type 2 diabetes is the predominant form of diabetes,[1] characterized by reduced function of β-cells[2]. The incidence of type 2 diabetes in China was 10.9% in 2013[3]. An examination comprising 6,043 Chinese patients showed that just 32.1% reached the glycated hemoglobin (HbA1c) target goal of <7.0%[4,5]. Effective patient-centered strategies for the treatment of type 2 diabetes should balance the benefits of glycemic control, and the threat of weight gain (WG) and hypoglycemia[6,7]. Composite end-point (CE) measures are commonly used in several therapeutic areas, the use of clinically important CEs

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Table 1 | Baseline characteristics and demographics

Characteristic	AWARD-CHN1 study			AWARD-CHN2 study		
	DU 1.5 mg	DU 0.75 mg	GLIM	DU 1.5 mg	DU 0.75 mg	GLAR
n (mITT)	184	186	186	200	196	195
Sex, female (%)	41	42	41	42	39	37
Age (years)	52.8	53.8	52.7	54.5	54.1	55.0
Weight (kg)	69.7	70.7	69.1	71.9	73.2	72.5
Diabetes duration (years)	4.0	3.2	3.6	7.7	7.8	8.2
BMI (kg/m^2)	25.5	26.0	25.3	25.8	26.2	26.0
HbA1c (%)	8.0	8.0	7.9	8.4	8.3	8.3
HbA1c (mmol/mol)	64	64	63	68	67	67
FBG (mmol/L)	9.5	9.3	9.4	9.6	9.7	9.9
FBG (mg/dL)	171	167	169	173	175	178

Data are the mean, unless otherwise indicated. AWARD- CHN1, Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) Chinese 1 (CHN1); AWARD-CHN2, Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) Chinese 2 (CHN2); BMI, body mass index; DU, dulaglutide; FBG, fasting blood glucose; GLAR, insulin glargine; GLIM, glimepiride; HbA1c, glycated hemoglobin; mITT, modified intent-to-treat.

that include glycemic control with WG and hypoglycemia allows a more patient-centered approach in the treatment of type 2 diabetes[8,9].

Glucagon-like peptide-1 receptor agonist (GLP-1RAs) is known to trigger insulin secretion based on blood glucose level, and offer glycemic control with the relatively reduced threat of WG and hypoglycemia[7,10]. Dulaglutide (DU) is a long-acting GLP-1RA that is administered once a week, and has been approved for clinical use in the management of type 2 diabetes. In the global Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) program, the efficacy and safety of DU were evaluated in Caucasian type 2 diabetes patients, and a considerably greater number of patients that attained the CE of HbA1c <7.0%, with no risk of adverse events, such as weight gain or hypoglycemia, as compared with standard antidiabetic therapies were reported[9]. However, it is not known whether DU has a similar effect on the CE among Chinese type 2 diabetes patients. Thus, the present post-hoc analysis of two-phase III randomized trials aimed to assess the effect of DU (1.5/0.75 mg) in comparison with glimepiride (GLIM) or insulin glargine (GLAR) on the CE of HbA1c <7.0%, without WG (≤0 kg), and hypoglycemia (≤3.9 mmol/L) in Chinese type 2 diabetes patients after 26 or 52 weeks of treatment.

METHODS

Design and patients

Data from two randomized, multinational, parallel-arm, non-inferiority, phase III trials (AWARD-CHN1 study [NCT01644500][11] and AWARD-CHN2 study [NCT01648582][12]) of DU in type 2 diabetes patients were analyzed. Both studies enrolled adult type 2 diabetes patients, and were intended to assess the non-inferiority and superiority of DU with active comparators. Institutional ethics committee approval was obtained for both studies, and written informed consent was given for each patient before participation. Both the AWARD trials received ethical committee approval before the start of study, and written informed consent was obtained from each patient before enrollment. Both the AWARD trials were carried out as per the ethical principles described in the Declaration of Helsinki and other applicable regulatory guidelines.

CEs

The primary CE of the present post-hoc analysis was the number of patients from both AWARD trials reaching HbA1c <7.0% without WG, and hypoglycemia after 26 and 52 weeks of treatment. Secondary CE included the number of patients reaching HbA1c <7.0% without WG and HbA1c <7.0% without hypoglycemia.

Statistical analysis

Data of the randomized patients from both the AWARD trials who received a single dose of study treatment, and had HbA1c assessment before and after treatment (on at least one post-treatment visit) were analyzed. Post-baseline missing data were substituted using the last observation carried forward method. Primary and secondary CEs were analyzed using Fisher's exact test. Statistical analysis was carried out using SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Disposition and patient characteristics

A total of 1147 Chinese type 2 diabetes patients were included in this post-hoc analysis (NCT01644500 = 556; NCT01648582 = 591). The patient characteristics are presented in Table 1. Apart from the duration of diabetes, patient characteristics in each study were comparable across the study treatments. The average daily doses (standard deviation) of GLIM and GLAR were 2.51 (0.86) mg and 21.0 (12.39) IU at week 26, respectively.

HbA1c <7.0%

A considerably larger number of patients attained an HbA1c target of <7.0% for both the doses of DU versus GLIM

Table 2 | Glycated hemoglobin, weight, hypoglycemia and composite endpoint

Treatment	ΔHbA1c (%)	HbA1c <7%[†] (% of patients)	Δ Weight (kg)	No weight gain (% of patients)	No hypoglycemia[‡] (% of patients)	Achieving composite end-point (% of patients)
AWARD-CHN1 study 26 weeks						
DU 1.5 mg	−1.46***	71.7**	−1.51***	66.8***	96.7***	47.8***
DU 0.75 mg	−1.25**	63.4	−0.95***	62.4***	98.4***	39.2***
Glimepiride	−0.92	57.5	0.92	41.9	83.3	19.9
AWARD-CHN2 study 26 weeks						
DU 1.5 mg	−1.67***	66.0***	−1.30***	66.0***	86.0*	39.5***
DU 0.75 mg	−1.31*	54.1**	−0.85***	65.3***	87.2*	30.1***
Insulin glargine	−1.11	39.0	1.00	35.4	77.9	14.9
AWARD-CHN2 study 52 weeks						
DU 1.5 mg	−1.38***	52.0***	−0.82***	59.0***	83.0*	26.0***
DU 0.75 mg	−1.00*	46.4***	−0.66***	60.7***	84.2**	23.0***
Insulin glargine	−0.79	29.2	1.34	31.3	72.3	6.7

Data are least-squares means, change (Δ) in glycated hemoglobin (HbA1c) and Δ weight (mixed-effect model for repeated measures), HbA1c <7.0% (mixed-effect model for repeated measures, last observation carried forward, Fisher's exact test), no weight gain, no hypoglycemia, composite end-points (mixed-effect model for repeated measures, Fisher's exact test) versus active comparator: $^{*}P < 0.05$ $^{**}P < 0.01$ $^{***}P < 0.001$. [†]53 mmol/mol. [‡]Hypoglycemia with blood glucose ≤3.9 mmol/L or any report of severe hypoglycemia. AWARD- CHN1, Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) Chinese 1 (CHN1); AWARD-CHN2, Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) Chinese 2 (CHN2); DU, dulaglutide.

($P < 0.01$) and GLAR ($P < 0.001$) at 26 and 52 weeks after treatment, except for DU 0.75 mg versus GLIM at 26 weeks (Table 2). The changes in baseline HbA1c and bodyweight, including the number of patients with an HbA1c target of <7.0% and no hypoglycemia incidence at week 26 and 52, are shown in Table 2 for both the studies.

HbA1c <7.0%, without weight gain and hypoglycemia

At week 26, in each analyzed trial, 40–48% of patients received DU (1.5 mg), 30–39% of patients received DU (0.75 mg) and 15–20% of patients treated with active comparators reached a target HbA1c of <7.0%, without WG and hypoglycemia (Table 2; Figure 1). At 52 weeks, 26% of patients that received DU (1.5 mg), 23% of patients that received DU (0.75 mg) and 7% of that patients received GLAR attained an HbA1c target of <7.0% without WG and hypoglycemia (Table 2; Figure 1). A significantly greater number of patients attained the CE with DU (1.5/0.75 mg) versus GLIM and GLAR after 26 or 52 weeks ($P < 0.001$ for each comparison; Table 2). Furthermore, the numbers of patients who attained the CE with DU (1.5/0.75 mg) and GLAR were lower after 52 weeks of treatment as compared with 26 weeks.

HbA1c <7.0% and no weight gain

At week 26, in each analyzed trial, 49–50% of patients received DU (1.5 mg), 37–40% of patients received DU (0.75 mg) and 19–29% of patients treated with active comparators attained a target HbA1c of <7.0% without WG (Figure 2a). A significantly greater number of patients attained the CE with DU (1.5/0.75 mg) versus GLIM ($P < 0.001$ and $P = 0.022$, respectively), as well as versus GLAR (both $P < 0.001$). At 52 weeks, 37% of patients that received DU 1.5 mg, 29% of patients that received

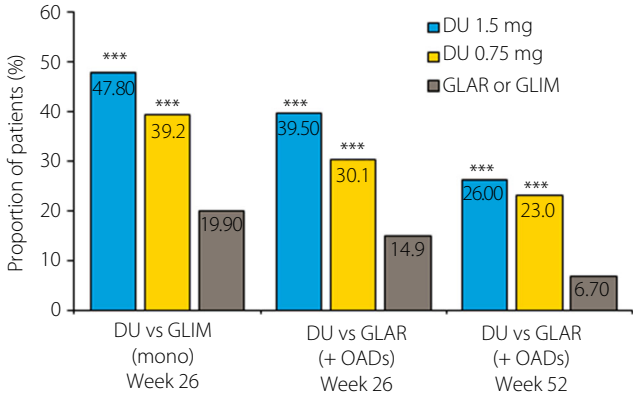

Figure 1 | Proportion of patients achieving the composite end-point of glycated hemoglobin <7%, no weight gain and no hypoglycemia. Hypoglycemia with blood glucose ≤3.9 mmol/L or any report of severe hypoglycemia, modified intention-to-treat and Fisher's exact test versus active comparator: $^{***}P < 0.001$. DU, dulaglutide; GLAR, insulin glargine; GLIM, glimepiride; HbA1c, glycated hemoglobin; mono, monotherapy; OAD, oral antihyperglycemic drug.

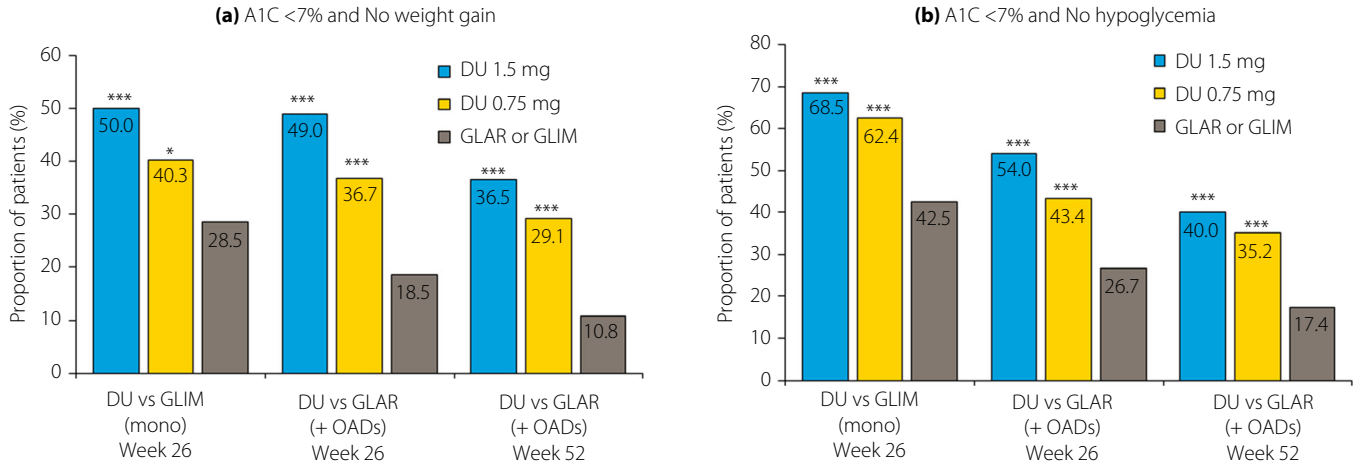

Figure 2 | Proportion of patients achieving the composite end-point of (a) glycated hemoglobin <7.0% and no weight gain, (b) glycated hemoglobin <7.0% and no hypoglycemia. Hypoglycemia with blood glucose ≤3.9 mmol/L or any report of severe hypoglycemia, modified intention-to-treat, Fisher's exact test versus active comparator: *$P < 0.05$, ***$P < 0.001$. DU, dulaglutide; GLAR, insulin glargine; GLIM, glimepiride; mono, monotherapy; OAD, oral antihyperglycemic drug.

DU 0.75 mg and 11% of patients that received GLAR attained the CE (Figure 2a). A considerably greater number of patients attained the CE with DU (1.5/0.75 mg) versus GLAR (both $P < 0.001$). At 52 weeks, the numbers of patients who attained the CE with DU (1.5/0.75 mg) and GLAR were lower, as compared with 26 weeks.

HbA1c <7.0% and no hypoglycemia

In each analyzed trial, 54–69% of patients that received DU 1.5 mg, 43–62% of patients that received DU 0.75 mg and 27–43% of patients treated with active comparators attained a target HbA1c of <7.0% without hypoglycemia at week 26 (Figure 2b). A considerably larger number of patients attained the CE with DU (1.5/0.75 mg) versus GLIM, as well as versus GLAR (all $P < 0.001$). At 52 weeks, 40% of patients that received DU 1.5 mg, 35% of patients that received DU 0.75 mg and 17% of patients that received GLAR attained the CE (Figure 2b). A considerably larger number of patients attained the CE with DU (1.5/0.75 mg) versus GLAR (both $P < 0.001$). Compared with 26 weeks, the proportions of patients who attained the CE with DU (1.5/0.75 mg) and GLAR were lower at 52 weeks.

DISCUSSION

The use of CE to concurrently evaluate clinical benefits (glycemic control) along with the treatment-related risk (weight gain and hypoglycemia) is a patient-centered approach in managing type 2 diabetes, and is also a commonly used assessment tool to assess treatment choices for the management of type 2 diabetes[8,13]. The International Association of Diabetes (the USA and Europe) recommend glucose-dropping agents based on the efficacy (HbA1c reduction) and safety (lower risk of weight gain and hypoglycemia)[14,15]. The efficacy and safety of treatment modalities can be defined more systematically using the clinically important CE, especially when more than one desired therapeutic response of treatment is essential[16]. The present post-hoc analysis is the first analysis to compare the effect of DU (1.5/0.75 mg) with GLIM or GLAR on the CE of HbA1c <7.0%, without WG and hypoglycemia in Chinese type 2 diabetes patients. This analysis showed that, compared with GLIM or GLAR, a significantly larger number of patients treated with DU attained the CE. In both included studies at 26 or 52 weeks, 26–47.8% of patients attained the CE with DU (1.5 mg), with a significantly larger number compared with GLIM (19.9%) or GLAR (6.7–14.9%). Also, 23–39.2% of patients attained the CE with DU (0.75 mg), with a considerably larger number than GLIM or GLAR. Furthermore, the numbers of patients who attained the CE with DU (1.5/0.75 mg) and GLAR were lower after 52 weeks of treatment as compared with 26 weeks. This was due to the tail-raising of HbA1c reduction and weight reduction at week 26, with a continuing low hypoglycemic rate at weeks 26 and 52, associated with DU[17,18].

Post-hoc analyses of the global AWARD program (AWARD-1 to 3, 5 and 6), which comprised mainly Caucasian type 2 diabetes patients, showed that 37–58% of patients that received DU 1.5 mg attained the CE, with considerably larger proportions compared with active comparators[9]. Furthermore, a considerably larger number of patients attained the CE with DU (0.75 mg), as compared with sitagliptin or GLAR[11]. A clinical trial program of liraglutide showed that 40% of patients treated with liraglutide 1.8 mg, 32% of patients treated with liraglutide 1.2 mg and 6–25% of patients treated with active comparators attained the CE of HbA1c <7.0% without WG and hypoglycemia[19]. As there were considerable alterations in background treatments and hypoglycemia definitions in the previous and present analysis, head-to-head comparisons between previous results and the present results are not

appropriate because of differences in background therapies and in definitions of hypoglycemia. In AWARD-2, background therapies comprised of metformin and GLIM, which is similar in AWARD-CHN2 with metformin and/or a sulfonylurea. At 26 weeks, the type 2 diabetes patients receiving DU in AWARD-2 were similar to those who attained the CE of HbA1c <7.0%, without WG and hypoglycemia in AWARD-CHN2.

In both Chinese studies[11,12], DU (1.5/0.75 mg) has an acceptable safety and tolerability profile, which is similar to the GLP-1RA class of drugs[11,12,19–21], suggesting a satisfactory risk-to-benefit ratio for DU. The findings of the present post-hoc analysis are similar to the findings from global studies (AWARD trials) with DU and with published studies of other GLP-1RAs[20,21].

The present post-hoc analysis had some limitations. The pooling of data or integrated meta-analysis was not feasible because of the confounding effect that background medications can have on weight change and the incidence of hypoglycemia. In addition, this analysis was not designed to assess the relative weighting of the components of the CE or the role of composite measures in determining long-term outcomes. Thus, the present CE might be more appropriate for conveying prompt treatment decisions.

Dulaglutide is an effective therapeutic alternative for Chinese type 2 diabetes patients. Compared with GLIM or GLAR, significantly greater proportions of patients on DU attained the HbA1c target of <7.0% without WG or hypoglycemia. These outcomes are similar to global studies with DU and studies with the other GLP-1RA class.

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DISCLOSURE

BZ and JNH are employees of Eli Lilly and Company. LQG was an employee of Eli Lilly and Company at the time of manuscript preparation. The other authors declare no conflict if interest.

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