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A 1-year safety study of dulaglutide in Japanese patients with type 2 diabetes on a single oral hypoglycemic agent: an open-label, nonrandomized, phase 3 trial

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Abstract. The goal of this study was to assess the safety and efficacy of 0.75 mg of dulaglutide, a once weekly glucagon-like peptide-1 receptor agonist, in Japanese patients with type 2 diabetes (T2D) on a single oral hypoglycemic agent (OHA). In this phase 3, nonrandomized, open-label, parallel-group, 52-week study, safety and efficacy of once weekly dulaglutide 0.75 mg were assessed in Japanese patients with T2D on a single OHA (sulfonylureas [SU], biguanides [BG], α-glucosidase inhibitors [AGI], thiazolidinedione [TZD], or glinides [GLN]). A total of 394 patients were treated with study drug, and 92.9% completed the 52-week treatment period. The most frequent treatment-emergent adverse events were nasopharyngitis and gastrointestinal disorders, including constipation, diarrhea, and nausea. Incidences of hypoglycemia varied across the combination therapy groups: incidence was greater in patients receiving SU compared with other combinations. No severe hypoglycemic episodes occurred during the study. Increases from baseline in pancreatic and total amylase, lipase, and pulse rate were observed in all 5 combination therapy groups. Significant reductions from baseline in HbA1c were observed in all 5 combination therapy groups (–1.57% to –1.69%, $p < 0.001$ for all). Mean body weight changes from baseline varied across the combination therapy groups: a significant increase was observed in combination with TZD, there were no significant changes in combination with SU or GLN, and significant reductions were observed in combination with BG or AGI. Once weekly dulaglutide 0.75 mg in combination with a single OHA was overall well tolerated and improved glycemic control in Japanese patients with T2D.

Key words: Phase 3 study, GLP-1 receptor agonist, Dulaglutide, Type 2 diabetes

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) is an endogenous incretin hormone that is rapidly secreted by intestinal L-cells in response to food ingestion. GLP-1 stimulates postprandial insulin secretion, inhibits glucagon secretion, and slows gastric emptying [1]. The acute administration of GLP-1 induces satiety and reduces food intake in subjects with and without diabetes [2, 3]. Several GLP-1 receptor agonists have been developed or are in development for the treatment of type 2 diabetes (T2D) [4–6]. As of June 2015, four GLP-1 receptor agonists (liraglutide [7], exenatide twice daily and once weekly [8, 9], and lixisenatide [10]) have been launched in Japan.

Dulaglutide is a long-acting GLP-1 receptor agonist

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Abbreviations: ADA, antidrug antibodies; AGI, α-glucosidase inhibitors; BG, biguanides; BMI, body mass index; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; DU 0.75, once weekly dulaglutide 0.75 mg; ECG, electrocardiogram; FAS, Full Analysis Set; FSG, fasting serum glucose; GLN, glinides; GLP-1, glucagon-like peptide-1; HOMA2-%B, updated Homeostasis Model Assessment of beta cell function; HOMA2-%S, updated Homeostasis Model Assessment of insulin sensitivity; JDS, Japan Diabetes Society; LOCF, last observation carried forward; MACE, major adverse cardiovascular event; OHA, oral hypoglycemic agent; SGLT2, sodium/glucose cotransporter 2; SMBG, self-monitored blood glucose; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinedione; ULN, upper limit of normal

that mimics some of the effects of endogenous GLP-1; it is administered as a subcutaneous injection once weekly. The 0.75 mg and 1.5 mg doses have been approved in the United States and the European Union, and the 0.75 mg dose (DU 0.75) has been approved in Japan for the treatment of T2D [11–13]. Dulaglutide has been modified to render the molecule more stable against dipeptidyl peptidase-4 (DPP-4) inactivation, increase the solubility of the peptide, reduce immunogenic potential, and increase the duration of its pharmacologic activity [14]. The pharmacokinetic half-life of DU 0.75 is approximately 4.5 days, and the maximum dulaglutide plasma concentration is observed approximately 2 days after subcutaneous administration in Japanese patients, which supports once weekly dosing (data not shown). In clinical trials in patients with T2D conducted outside of Japan, dulaglutide 1.5 mg once weekly has shown superiority to metformin, sitagliptin, insulin glargine, and exenatide twice daily and non-inferiority to liraglutide, all based on changes in HbA1c, and has been associated with reductions in body weight [15–19]. In phase 3 clinical trials in patients with T2D in Japan, DU 0.75 has shown superiority to insulin glargine and non-inferiority to liraglutide 0.9 mg based on changes in HbA1c after 26 weeks of treatment [20, 21].

Although dulaglutide is not an oral hypoglycemic agent (OHA), this study was conducted in accordance with the Guideline for Clinical Evaluation of OHA in Japan [22]. Based on this guideline, the primary objective of this study was to assess the safety and tolerability of once weekly DU 0.75 in combination with a single OHA over 52 weeks of treatment.

The 5 OHAs that DU 0.75 was added onto in this study were as follows: sulfonylureas (SU), biguanides (BG), α-glucosidase inhibitors (AGI), thiazolidinedione (TZD), and glinides (GLN).

Materials and Methods

Study design and patients

This was a 52-week, multicenter, nonrandomized, outpatient, open-label, phase 3 study to assess the long-term safety and efficacy of DU 0.75 in patients with T2D who had inadequate glycemic control with a single OHA.

The study had 4 periods: screening (2 weeks), lead-in (2 weeks), treatment (52 weeks), and safety follow-up (30 days). The study was conducted from December 2011 to December 2013 at 34 sites in Japan and was registered at ClinicalTrials.gov (NCT01468181).

Japanese male and female patients ≥20 years old who had been diagnosed with T2D and had a screening HbA1c ≥7.0% to ≤11.0% were eligible; they were required to be taking SU, BG, AGI, TZD, or GLN monotherapy for at least 3 months before screening at doses that were stable for at least 8 weeks before screening. Key exclusion criteria included patients with type 1 diabetes; patients previously treated with any GLP-1 receptor agonist or insulin within 3 months prior to screening; patients undergoing chronic systemic glucocorticoid therapy; and patients who had a clinically significant gastric emptying abnormality, cardiovascular (CV) disease, liver disease, renal disease, active or untreated malignancy, history of chronic or acute pancreatitis, obvious clinical signs or symptoms of pancreatitis, or self or family history of medullary C-cell hyperplasia, focal hyperplasia, or medullary thyroid carcinoma. Hypoglycemia was defined as blood glucose concentration of ≤70 mg/dL and⁄or symptoms and⁄or signs attributable to hypoglycemia. Severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer therapy [23].

A common protocol was approved at each site by an institutional review board, and the study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Each patient provided written informed consent prior to participation.

Study treatments

DU 0.75 was given once weekly as a subcutaneous injection. Throughout the study, patients were maintained on stable doses of their usual OHA (SU, BG, AGI, TZD, or GLN) unless dose modifications were required due to hypoglycemia or persistent hyperglycemia.

Study endpoints and assessments

Safety measures evaluated were treatment-emergent adverse events, vital signs (blood pressure and pulse rate), electrocardiograms (ECGs), laboratory tests, dulaglutide antidrug antibodies (ADAs), and hypoglycemia. Efficacy measures evaluated were HbA1c (changes from baseline), proportions of patients who achieved HbA1c <7.0% or ≤6.5%, fasting serum glucose (FSG; changes from baseline), 7-point self-monitored blood glucose (SMBG) profiles (changes from baseline), β-cell function and insulin sensitivity as esti-

mated with updated Homeostasis Model Assessment [24] (HOMA2-%B and HOMA2-%S [each calculated with both fasting insulin and C-peptide], respectively; changes from baseline), and body weight (changes from baseline).

Deaths, nonfatal CV adverse events, cardiac biomarkers, and possible cases of pancreatitis (patients with severe abdominal pain or serum amylase and/or lipase ≥3 times the upper limit of normal [ULN]) were adjudicated by independent committees of expert physicians.

Statistical analyses

Because this study was nonrandomized, no between-group hypothesis testing was conducted for safety or efficacy measures, and statistical tests of within-group changes from baseline for efficacy parameters were conducted for reference only. For these reasons, statistically-derived power calculations were not used to determine sample size. Sample size was based on the Japanese Guideline for Clinical Evaluation of OHA [22] for safety assessment: at least 100 patients treated for 1 year in combination with SU (based on SUs having a higher hypoglycemia risk compared with other OHAs) and at least 50 patients treated for 1 year in combination with each of the other 4 agents. Taking into account the expected overall dropout rate of approximately 17%, a total of 365 patients was planned to be enrolled: approximately 60 patients in each of the DU 0.75+BG, DU 0.75+AGI, DU 0.75+TZD, and DU 0.75+GLN groups, and approximately 120 patients in the DU 0.75+SU group.

The Full Analysis Set (FAS), defined as all patients enrolled who took at least 1 dose of study drug, was used for safety and efficacy reporting. For laboratory tests, vital signs, ECGs, and efficacy measures, within-group changes from baseline at each time point were assessed by *t*-tests at the level of 0.05. *T*-tests at individual time points were based on patients with nonmissing baseline data and nonmissing data at the time point. Adjustments for multiplicity were not used for *t*-tests at multiple time points. At weeks 26 and 52, last observation carried forward (LOCF) imputation was also used for both safety and efficacy assessments with *t*-tests. Observed values and changes from baseline in laboratory measurements were summarized by combination therapy group at each scheduled visit as well as at endpoint (LOCF). Statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Patients

A total of 452 patients entered the study, with 394 (DU 0.75+SU, 131; DU 0.75+BG, 61; DU 0.75+AGI, 65; DU 0.75+TZD, 66; DU 0.75+GLN, 71) patients assigned to treatment (enrolled). All enrolled patients received at least 1 dose of study drug and comprised the FAS. A total of 366 patients (92.9%) completed the 52-week treatment period, and 28 patients (7.1%) were discontinued from the study early. The most common reasons for discontinuation overall were adverse event (4.8%) and protocol violation (1.0%).

The mean ± standard deviation (SD) age overall was 57.4 ± 11.0 years (Table 1). All patients were Japanese. The majority (75%) were male. The mean duration of T2D was 7.7 ± 6.3 years. The mean HbA1c was 8.5 ± 1.1%, and the mean FSG was 172.8 ± 41.6 mg/dL. Mean body weight was 71.4 ± 13.3 kg, and mean body mass index (BMI) was 25.9 ± 3.7 kg/m^2. Mean duration of T2D was longest in patients receiving SU (9.4 years). Mean age was lowest in patients receiving BG (52.7 years). Mean BMI was highest in patients receiving TZD or BG (27.0 and 27.1 kg/m^2, respectively). Mean HbA1c was highest in patients receiving GLN or SU (8.6% and 8.9%, respectively). The mean dose of SU at baseline was 2.5 mg glimepiride equivalent.

Safety

No deaths occurred during the study. The incidence of treatment-emergent adverse events during the study ranged from 70.8% (DU 0.75+AGI) to 85.5% (DU 0.75+SU). Nasopharyngitis was the most frequent treatment-emergent adverse event overall, followed by constipation, diarrhea, and nausea (Table 2). In total, 19 patients (4.8%) experienced ≥1 serious adverse event through the treatment period (Table 2). The incidence of serious adverse events during the study ranged from 1.5% (DU 0.75+TZD) to 6.9% (DU 0.75+SU). One additional patient (DU 0.75+GLN) experienced a serious adverse event during the follow-up period. Serious adverse events are summarized in Supplementary Table 1. The only serious adverse event reported by more than 1 patient overall was large intestine polyp (2 patients: DU 0.75+BG, 1; DU 0.75+GLN, 1). Serious adverse events for which study drug causality was not excluded by the investigator were bile duct stone, edema, and adenocarcinoma gastric, each of which occurred in separate patients. Five patients were dis-

Table 1 Patient characteristics at baseline

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71	Total N=394
Sex						
Women	36 (27.5)	21 (34.4)	10 (15.4)	14 (21.2)	17 (23.9)	98 (24.9)
Men	95 (72.5)	40 (65.6)	55 (84.6)	52 (78.8)	54 (76.1)	296 (75.1)
Age (years)	58.7 (11.6)	52.7 (10.2)	59.1 (10.5)	56.4 (10.5)	58.2 (10.3)	57.4 (11.0)
≥65 years	44 (33.6)	6 (9.8)	20 (30.8)	13 (19.7)	18 (25.4)	101 (25.6)
Weight (kg)	70.0 (12.6)	74.5 (12.0)	70.2 (12.5)	75.2 (15.6)	68.7 (12.9)	71.4 (13.3)
BMI (kg/m^2)	25.7 (3.6)	27.1 (3.7)	25.4 (3.6)	27.0 (3.9)	24.9 (3.5)	25.9 (3.7)
Diabetes duration (years)	9.4 (6.8)	5.8 (4.4)	8.1 (7.0)	7.4 (6.7)	6.1 (4.8)	7.7 (6.3)
HbA1c (%)	8.9 (1.1)	8.2 (0.9)	8.1 (1.0)	8.4 (1.2)	8.6 (1.2)	8.5 (1.1)
FSG (mg/dL)	181.6 (43.6)	160.8 (35.8)	165.6 (40.0)	165.2 (43.2)	180.7 (37.8)	172.8 (41.6)
Seated vital signs						
SBP (mmHg)	134.8 (13.6)	124.7 (10.7)	129.7 (14.9)	129.0 (11.9)	132.4 (14.6)	131.0 (13.7)
DBP (mmHg)	81.5 (9.4)	79.4 (9.0)	79.8 (8.6)	81.4 (9.1)	80.9 (9.2)	80.8 (9.1)
Pulse rate (bpm)	72.8 (10.1)	73.3 (9.6)	72.3 (10.2)	71.2 (10.3)	73.7 (12.0)	72.7 (10.4)

AGI, α-glucosidase inhibitor; BG, biguanide; BMI, body-mass index; DBP, diastolic blood pressure; DU 0.75, 0.75 mg dulaglutide once weekly; FSG, fasting serum glucose; GLN, glinide; N, number of patients in full analysis set; SBP, systolic blood pressure; SU, sulfonylurea; TZD, thiazolidinedione. Data are numbers (%) or mean (SD).

continued from the study due to serious adverse events: 3 in the DU 0.75+SU group (acute myocardial infarction, edema, and adenocarcinoma gastric) and 2 in the DU 0.75+AGI group (ovarian neoplasm and cholangitis). A total of 19 patients (4.8%) were discontinued from the study due to an adverse event through the treatment period (Table 2).

A total of 10 nonfatal CV events were adjudicated for a total of 6 patients (DU 0.75+SU, 6 events in 3 patients; DU 0.75+AGI, 4 events in 3 patients). Events in 5 patients were confirmed as CV events (DU 0.75+SU, congestive cardiac failure, acute myocardial infarction, and coronary angioplasty in 1 patient; cerebral infarction in 1 patient; coronary arterial stent insertion and angina unstable in 1 patient; DU 0.75+AGI, myocardial ischemia and coronary artery bypass in 1 patient and percutaneous coronary intervention in 1 patient). One event, the serious adverse event of myocardial infarction, was confirmed upon adjudication as a major adverse CV event (MACE); the investigator did not consider this event to be possibly related to study drug.

Median increases from baseline in amylase and lipase were observed in all 5 combination therapy groups (Table 2). Percentages of patients with treatment-emergent abnormal changes in total amylase ranged from 7.5% (DU 0.75+SU) to 14.7% (DU 0.75+GLN). Percentages of patients with treatment-emergent abnormal changes in lipase ranged from 23.3% (DU 0.75+TZD) to 43.5% (DU 0.75+AGI). Three and 16 patients, respectively, had total amylase or lipase >3×ULN during the study. Two cases of pancreatitis were confirmed on adjudication, both in the DU 0.75+SU group (1 patient was a 73-year-old female with BMI of 22.5 kg/m^2 and the other patient was a 45-year-old male with BMI of 30.5 kg/m^2). In the former case, pancreatic enzyme increases were thought to have been iatrogenically induced by an endoscopic ultrasound/fine needle aspiration procedure for tumor examination; the results of the fine needle aspiration were not reported to the sponsor, but the patient continued treatment in the study for approximately 10 months after the procedure and completed the study with no additional pancreatic-related complaints or adverse events. In the latter case, there were no typical abdominal symptoms of pancreatitis related to the lipase increase.

No median changes from baseline in serum calcitonin were observed in any combination therapy group at week 52 (LOCF), and all postbaseline calcitonin values were within normal limits. No treatment-emergent thyroid-related adverse events were observed.

A total of 19 patients (4.8%) experienced at least 1 treatment-emergent adverse event related to injection site reactions through 52 weeks. All of the treatment-emergent injection site adverse events were of mild intensity, except for 1 moderate-intensity injection site reaction, which led to discontinuation from the

Table 2 Safety assessments and vital signs

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	9 (6.9)	3 (4.9)	4 (6.2)	1 (1.5)	2 (2.8)
Patients with at least one treatment-emergent adverse event	112 (85.5)	51 (83.6)	46 (70.8)	53 (80.3)	52 (73.2)
Treatment-emergent adverse events (≥5% of patients in any group)[§]					
Nasopharyngitis	31 (23.7)	16 (26.2)	11 (16.9)	16 (24.2)	16 (22.5)
Constipation	20 (15.3)	3 (4.9)	8 (12.3)	3 (4.5)	5 (7.0)
Diarrhea	13 (9.9)	9 (14.8)	3 (4.6)	5 (7.6)	7 (9.9)
Nausea	17 (13.0)	2 (3.3)	4 (6.2)	5 (7.6)	3 (4.2)
Lipase increased	11 (8.4)	6 (9.8)	6 (9.2)	3 (4.5)	2 (2.8)
Back pain	8 (6.1)	2 (3.3)	2 (3.1)	6 (9.1)	1 (1.4)
Decreased appetite	10 (7.6)	3 (4.9)	3 (4.6)	1 (1.5)	2 (2.8)
Pharyngitis	7 (5.3)	2 (3.3)	3 (4.6)	6 (9.1)	0 (0.0)
Hypertension	5 (3.8)	3 (4.9)	4 (6.2)	2 (3.0)	3 (4.2)
Influenza	6 (4.6)	7 (11.5)	0 (0.0)	0 (0.0)	3 (4.2)
Vomiting	8 (6.1)	1 (1.6)	3 (4.6)	3 (4.5)	1 (1.4)
Bronchitis	10 (7.6)	1 (1.6)	0 (0.0)	2 (3.0)	2 (2.8)
Dyspepsia	6 (4.6)	2 (3.3)	1 (1.5)	0 (0.0)	5 (7.0)
Contusion	2 (1.5)	4 (6.6)	1 (1.5)	2 (3.0)	2 (2.8)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.1)	1 (1.4)
Patients discontinued from the study due to adverse event	8 (6.1)	1 (1.6)	6 (9.2)	2 (3.0)	2 (2.8)
Seated vital signs (mean change from baseline [SE])[‡]					
Systolic blood pressure (mmHg)	−1.9 (1.1)	0.9 (1.5)	−0.6 (1.7)	1.0 (1.3)	−2.1 (1.6)
Diastolic blood pressure (mmHg)	−0.7 (0.7)	0.5 (1.0)	−0.0 (1.1)	0.5 (0.9)	−1.1 (0.9)
Pulse rate (bpm)	2.8 (0.7)**	3.1 (0.9)*	1.7 (1.0)	1.8 (0.9)*	3.7 (0.8)**
ECG PR interval (ms)	1.8 (0.8)*	2.3 (1.3)	3.3 (1.4)*	0.8 (1.5)	1.6 (1.7)
Pancreatic enzymes (median change; minimum and maximum)[‡]					
Total amylase (U/L)	7.0 (−151, 74)*	5.0 (−34, 58)*	11.0 (−72, 245)**	4.0 (−24, 59)*	6.0 (−139, 97)
Lipase (U/L)	9.0 (−93, 73)**	6.0 (−15, 128)**	9.0 (−180, 629)	4.5 (−17, 51)**	5.0 (−43, 449)
Patients with treatment-emergent abnormal changes in pancreatic enzymes (>ULN)[‡‡]					
Total amylase	9/120 (7.5)	6/59 (10.2)	6/60 (10.0)	6/60 (10.0)	10/68 (14.7)
Lipase	46/118 (39.0)	16/56 (28.6)	27/62 (43.5)	14/60 (23.3)	23/65 (35.4)
Patients with pancreatic enzyme concentration >3×ULN					
Total amylase	1 (0.8)	0 (0.0)	1 (1.5)	1 (1.5)	0 (0.0)
Lipase	5 (3.8)	5 (8.2)	4 (6.2)	1 (1.5)	1 (1.4)
Treatment-emergent dulaglutide antidrug antibodies[¶]					
Dulaglutide antidrug Antibodies	1 (0.8)	0 (0.0)	1 (1.5)	3 (4.5)	4 (5.6)
Dulaglutide neutralising antidrug antibodies	1 (0.8)	0 (0.0)	1 (1.5)	3 (4.5)	4 (5.6)
nsGLP-1 neutralising antibodies	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	2 (2.8)

AGI, α-glucosidase inhibitor; BG, biguanides; DU 0.75, 0.75 mg dulaglutide once weekly; ECG, electrocardiogram; GLN, glinides; MedDRA, Medical Dictionary for Regulatory Activities. N, number of patients in full analysis set; nsGLP1, native sequence glucagon-like peptide-1; SU, sulfonylurea; TZD, thiazolidinedione; ULN, upper limit of normal. Data are numbers (%) unless otherwise specified. [§]MedDRA version 16.1. [‡]Data are last observation carried forward. [‡‡]Denominator is patients with a normal baseline and a postbaseline measurement. [¶]These values include all postbaseline observations including the safety follow-up. **denotes $p < 0.001$ for change from baseline within treatment group. *denotes $p < 0.05$ for change from baseline within treatment group.

study for 1 patient in the DU 0.75+SU group. A total of 6 patients experienced treatment-emergent adverse events that were considered hypersensitivity reactions: 5 patients experienced mild urticaria, and 1 patient experienced mild swelling of the face.

A total of 9 patients (2.3%) had at least 1 treatment-emergent dulaglutide ADA; all of these patients had treatment-emergent dulaglutide ADA that were dulaglutide neutralizing and native sequence GLP-1 cross-reactive (Table 2). All of these patients except for 1 completed 52 weeks of treatment. HbA1c increased from baseline to week 52 (LOCF) in 2 of the 9 patients (by 0.1 and 0.4%). None of these patients exhibited hypersensitivities or allergic reactions, though 2 experienced mild injection site pruritus.

Mean changes from baseline to week 52 (LOCF) in seated vital signs and ECG PR interval are presented in Table 2. There were no clinically relevant changes in seated systolic or diastolic blood pressure. Statistically significant mean increases from baseline in seated pulse rate were observed in 4 of the 5 combination therapy groups: mean changes ranged from 1.7 (DU 0.75+AGI) to 3.7 bpm (DU 0.75+GLN). Mean changes from baseline in ECG PR interval ranged from 0.83 msec (DU 0.75+TZD) to 3.25 msec (DU 0.75+AGI).

Table 3 summarizes incidence and rate (events/patient/30 days) of hypoglycemia through 52 weeks of treatment in this study. A total of 61 patients (15.5%) experienced hypoglycemia; the incidence was higher in the DU 0.75+SU group (33.6%) than in the other 4 combination therapy groups (range 3.3% to 9.9%). The mean ± SD hypoglycemia rate (events/patient/30 days) ranged from 0.00 ± 0.01 (DU 0.75+BG) to 0.10 ± 0.27 (DU 0.75+SU). No severe hypoglycemic episodes occurred during the study.

Efficacy

All 5 combination therapy groups had significant mean reductions from baseline in HbA1c ($p < 0.001$, all) beginning at week 14 that continued through week 52. The mean ± standard error (SE) change from baseline in HbA1c at week 26 (LOCF) overall was –1.77 ± 0.05%; changes ranged from –1.93 ± 0.09% (DU 0.75+SU) to –1.58 ± 0.11% (DU 0.75+BG; Table 4). The mean change from baseline in HbA1c at week 52 (LOCF) overall was –1.65 ± 0.05%; changes ranged from –1.69 ± 0.13% (DU 0.75+TZD) to –1.57 ± 0.11% (DU 0.75+BG). Fig. 1A plots mean HbA1c values (%) over time.

At week 26 (LOCF), 70.1% of patients overall achieved HbA1c <7.0%, and 51.8% achieved HbA1c ≤6.5%. Across the treatment groups, percentages of patients achieving HbA1c <7.0% ranged from 61.8% (DU 0.75+SU) to 81.5% (DU 0.75+AGI); percentages of patients achieving HbA1c ≤6.5% ranged from 35.1% (DU 0.75+SU) to 72.3% (DU 0.75+AGI; Table 4). At week 52 (LOCF), 65.5% of patients overall achieved HbA1c <7.0%, and 49.2% achieved HbA1c ≤6.5%. Across the treatment groups, percentages of patients achieving HbA1c <7.0% ranged from 48.9% (DU 0.75+SU) to 83.1% (DU 0.75+AGI), and percentages of patients achieving HbA1c ≤6.5% ranged from 31.3% (DU 0.75+SU) to 70.8% (DU 0.75+AGI).

All 5 combination therapy groups had significant mean reductions from baseline in FSG ($p < 0.001$, all) beginning at week 14 that continued through week 52. The mean ± SE change from baseline in FSG at week 26 (LOCF) overall was –43.9 ± 2.0 mg/dL; changes ranged from –37.9 ± 4.0 mg/dL (DU 0.75+BG) to –46.8 ± 4.2 mg/dL (DU 0.75+SU) and –46.8 ± 4.7 mg/dL (DU 0.75+AGI; Table 4). The mean ± SE change from baseline in FSG at week 52 (LOCF) overall was –42.6 ± 2.0 mg/dL; changes ranged from –36.0 ± 4.2 mg/dL (DU 0.75+BG) to –47.0 ± 4.7 mg/dL (DU 0.75+AGI). Fig. 1B plots mean FSG values (mg/dL) over time.

Treatment with dulaglutide in all 5 combination therapy groups resulted in statistically significant ($p < 0.05$) decreases from baseline in the following SMBG parameters at both weeks 26 (LOCF) and 52 (LOCF): individual 7-point SMBG profile values (data not shown), mean of 7-point blood glucose values, mean of all pre-meals blood glucose values, mean of all postprandial blood glucose values, breakfast 2-hour excursion, all meals 2hour excursion, and circadian variation (Supplementary Table 2). Fig. 2 plots mean 7-point SMBG profile values (mg/dL) at baseline and week 52 (LOCF).

Mean changes from baseline in body weight varied across the combination therapy groups (Table 4 and Fig. 1C). Mean ± SE changes from baseline at week 26 (LOCF) ranged from –1.22 ± 0.33 kg (DU 0.75+AGI) to 0.78 ± 0.30 kg (DU 0.75+TZD). Mean changes from baseline at week 52 (LOCF) ranged from –1.24 ± 0.42 kg (DU 0.75+AGI) to 1.02 ± 0.35 kg (DU 0.75+TZD).

Treatment with dulaglutide in all 5 combination therapy groups resulted in significant mean increases from baseline in HOMA2-%B (C-peptide and insu-

Table 3 Summary of hypoglycemia through week 52

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71
Incidence of hypoglycemia, n (%)					
Total hypoglycemia	44 (33.6)	2 (3.3)	4 (6.2)	4 (6.1)	7 (9.9)
Severe hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nocturnal hypoglycemia	9 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Rate of total hypoglycemia					
Mean (SD), events/patient/30 days	0.10 (0.27)	0.00 (0.01)	0.03 (0.18)	0.01 (0.03)	0.01 (0.04)

AGI, α-glucosidase inhibitor; BG, biguanides; DU 0.75, 0.75 mg dulaglutide once weekly; GLN, glinides; N, number of patients in full analysis set; SU, sulfonylurea; TZD, thiazolidinedione.

Table 4 Efficacy measures at week 26 (LOCF) and week 52 (LOCF)

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71
HbA1c (%)					
Week 26 (LOCF)					
Mean (SE)	6.94 (0.08)	6.64 (0.10)	6.44 (0.10)	6.64 (0.10)	6.79 (0.12)
Mean change from baseline (SE)	−1.93 (0.09)**	−1.58 (0.11)**	−1.67 (0.10)**	−1.71 (0.13)**	−1.80 (0.12)**
Week 52 (LOCF)					
Mean (SE)	7.20 (0.09)	6.66 (0.10)	6.46 (0.11)	6.66 (0.11)	6.95 (0.14)
Mean change from baseline (SE)	−1.67 (0.09)**	−1.57 (0.11)**	−1.65 (0.11)**	−1.69 (0.13)**	−1.65 (0.13)**
HbA1c targets					
Week 26 (LOCF), n (%)					
<7%	81 (61.8)	45 (73.8)	53 (81.5)	48 (72.7)	49 (69.0)
≤6.5%	46 (35.1)	33 (54.1)	47 (72.3)	40 (60.6)	38 (53.5)
Week 52 (LOCF), n (%)					
<7%	64 (48.9)	45 (73.8)	54 (83.1)	51 (77.3)	44 (62.0)
≤6.5%	41 (31.3)	35 (57.4)	46 (70.8)	38 (57.6)	34 (47.9)
FSG (mg/dL)					
Week 26 (LOCF)					
Mean (SE)	134.9 (3.3)	122.9 (3.2)	118.8 (3.3)	123.0 (3.2)	138.0 (4.0)
Mean change from baseline (SE)	−46.8 (4.2)**	−37.9 (4.0)**	−46.8 (4.7)**	−42.1 (4.5)**	−42.7 (3.9)**
Week 52 (LOCF)					
Mean (SE)	138.5 (3.3)	124.7 (2.8)	118.6 (2.8)	125.5 (5.4)	134.9 (4.3)
Mean change from baseline (SE)	−43.2 (3.8)**	−36.0 (4.2)**	−47.0 (4.7)**	−39.6 (5.0)**	−45.8 (4.0)**
Weight (kg)					
Week 26 (LOCF)					
Mean (SE)	70.04 (1.13)	73.79 (1.58)	68.99 (1.60)	75.93 (2.00)	68.92 (1.62)
Mean change from baseline (SE)	0.02 (0.22)	−0.74 (0.39)	−1.22 (0.33)**	0.78 (0.30)*	0.19 (0.25)
Week 52 (LOCF)					
Mean (SE)	70.12 (1.13)	73.66 (1.57)	68.97 (1.57)	76.17 (1.96)	68.77 (1.62)
Mean change from baseline (SE)	0.10 (0.24)	−0.87 (0.40)*	−1.24 (0.42)*	1.02 (0.35)*	0.04 (0.26)

AGI, α-glucosidase inhibitor; BG, biguanides; DU 0.75, 0.75 mg dulaglutide once weekly; FSG, fasting serum glucose; GLN, glinides; LOCF, last observation carried forward; N, number of patients in full analysis set; SU, sulfonylurea; TZD, thiazolidinedione. ** denotes $p < 0.001$ for change from baseline within treatment group. * denotes $p < 0.05$ for change from baseline within treatment group.

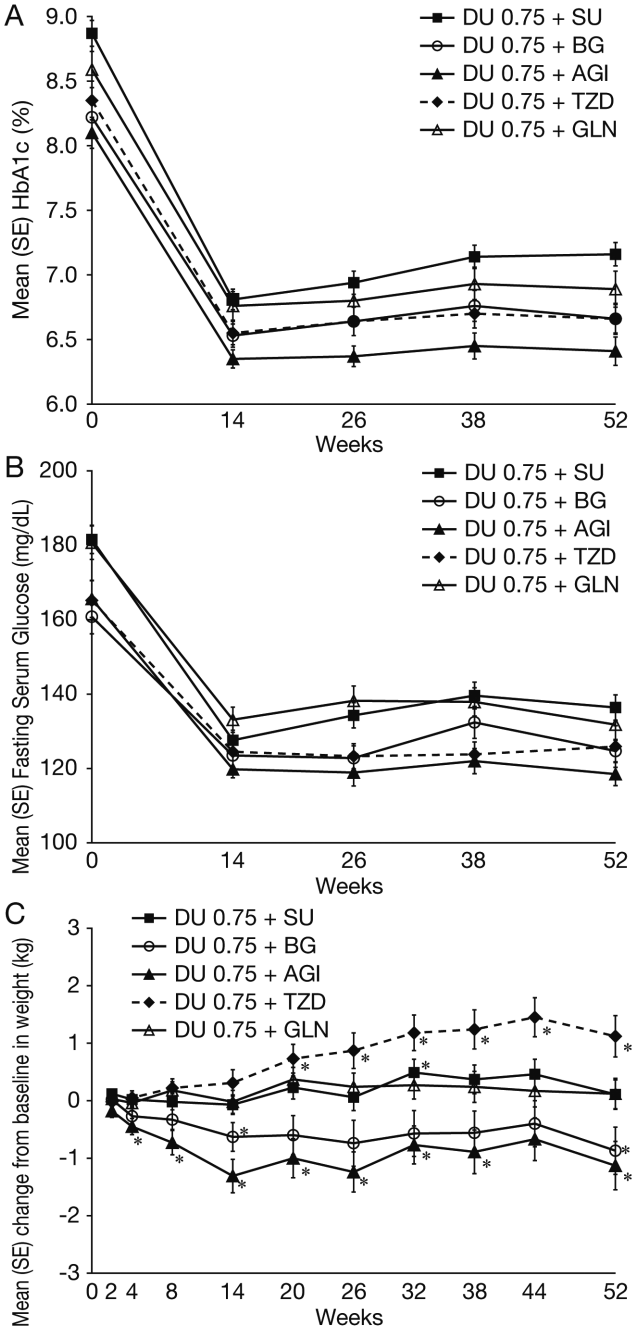

Fig. 1 HbA1c, FSG, and body weight. A. Mean (SE) HbA1c (%) values. Significant mean reductions from baseline in HbA1c ($p < 0.001$) were observed from week 14 through week 52 in all 5 combination therapy groups. B. Mean (SE) FSG (mg/dL) values. Significant mean reductions from baseline in FSG ($p < 0.001$) were observed from week 14 through week 52 in all 5 combination therapy groups. C. Mean (SE) changes from baseline in body weight (kg). AGI, α-glucosidase inhibitor. BG, biguanides. DU 0.75, 0.75 mg dulaglutide once weekly. FSG, fasting serum glucose, GLN, glinides. SU, sulfonylurea. TZD, thiazolidinedione. $^{*}p < 0.05$ for changes from baseline within treatment group.

lin) at weeks 26 (LOCF) and 52 (LOCF; $p < 0.001$, all; Supplementary Table 3). There were no statistically significant changes from baseline in HOMA2-%S (insulin) at weeks 26 (LOCF) or 52 (LOCF) in any combination therapy group. There was a significant mean increase from baseline in HOMA2-%S (C-peptide) in the DU 0.75+AGI group at week 52 (LOCF), but no statistically significant changes in any of the other combination therapy groups at weeks 26 (LOCF) or 52 (LOCF).

Discussion

Once weekly administration of DU 0.75 in combination with a single OHA was overall well tolerated. The incidence of discontinuations due to adverse events was low. There were no deaths during the study. Twenty patients experienced serious adverse events during the study. The most commonly reported treatment-emergent adverse events were nasopharyngitis and gastrointestinal disorders, such as constipation, diarrhea, nausea, and vomiting. The adverse event profile was generally consistent with other studies evaluating GLP-1 receptor agonists in Asian patients [25–30]. The incidence of diarrhea in the DU 0.75+BG group (14.8%) was higher than in the other combination therapy groups (range 4.6 to 9.9%). The incidence of constipation in the DU 0.75+AGI (12.3%) and DU 0.75+SU (15.3%) groups was higher than in the other combination therapy groups (range 4.5% to 7.0%). Finally, the incidence of nausea in the DU 0.75+SU group (13.0%) was higher than in the other combination therapy groups (range 3.3% to 7.6%). Although the reasons for the higher incidence of constipation and nausea in the DU 0.75+SU group remain unclear, diarrhea in the DU 0.75+BG group and constipation in the DU 0.75+AGI group were most likely caused by the mechanisms of action of the respective concomitant therapies.

No severe hypoglycemia was observed in this study. Incidence of total hypoglycemia over 52 weeks was more than 3 times higher in combination with SU (33.6%) than with any other concomitant therapy (range 3.3% to 9.9%). In order to avoid severe hypoglycemia in combination with SU, Japan Diabetes Society (JDS) recommends to reduce the SU dose (to ≤1.25 mg/day of glibenclamide, 40 mg/day of gliclazide, 2 mg/day of glimepiride) when starting incretin-related drugs in the recommendation for appropriate use of incretin drugs [31]. In this study, the mean dose of SU at baseline was 2.5 mg glimepiride equivalent,

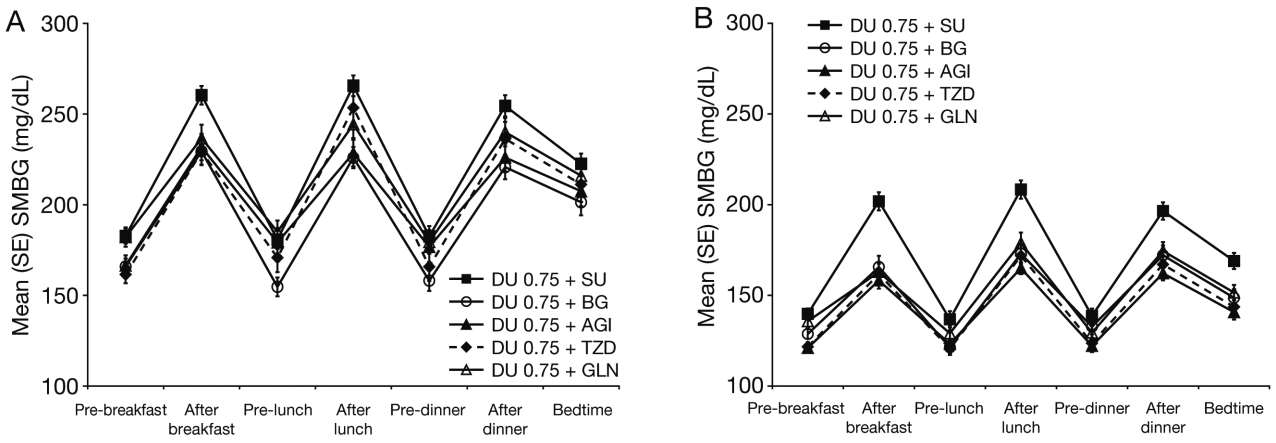

Fig. 2 Mean (SE) 7-point SMBG profiles (mg/dL) by time of day. A. At baseline. B. At week 52 (LOCF). AGI, α-glucosidase inhibitor. BG, biguanides. DU 0.75, 0.75 mg dulaglutide once weekly. GLN, glinides. LOCF, last observation carried forward. SMBG, self-monitored blood glucose. SU, sulfonylurea. TZD, thiazolidinedione. Significant mean reductions from baseline for all 7 SMBG time points ($p < 0.001$) were observed at week 52 (LOCF) in all 5 combination therapy groups.

nearly equal to the JDS recommendation.

Statistically significant increases from baseline in pulse rate were observed in 4 of the 5 combination therapy groups at week 52 (LOCF). These results are comparable to the data obtained for liraglutide 0.9 mg in phase 3 studies in Japan [25, 30] and for exenatide once weekly in a phase 3 study in Asian countries [27].

Consistent with previous reports in the GLP-1 receptor agonist class [19, 32] as well as other dulaglutide phase 3 studies in Japan [20, 21], increases in pancreatic enzymes were observed. Patients whose amylase or lipase levels exceeded 3×ULN were adjudicated, and 2 cases during the treatment period were adjudicated as pancreatitis. No patients developed acute pancreatitis with typical abdominal pain.

Significant mean reductions from baseline in HbA1c were observed from week 14 through week 52 in all 5 combination therapy groups ($p < 0.001$); the mean decrease overall at week 52 (LOCF) was approximately 1.7%. A total of 70.1% of patients overall achieved HbA1c target <7.0% at week 26 (LOCF) and 65.5% of patients achieved HbA1c target <7.0% at week 52 (LOCF); these results were consistent with other dulaglutide phase 3 studies in Japan [20, 21]. Treatment with dulaglutide in all 5 combination therapy groups resulted in significant improvements from baseline in secondary efficacy parameters, including FSG, 7-point SMBG profiles, and HOMA2-%B. Changes from baseline body weight at week 52 (LOCF) varied among the OHA combination therapy groups; reductions from baseline were observed in combination with BG (–0.87 kg) and AGI (–1.24 kg). The mechanism resulting in weight reduction with dulaglutide in combination with BG or AGI is unknown, but similar results were observed in a phase 3 study of liraglutide [33]. This study was a 52-week, open-label, parallel-group comparison study in which Japanese patients with type 2 diabetes who were inadequately controlled on a single OHA (AGI, GLN, metformin, or pioglitazone) had liraglutide 0.9 mg once daily or a second OHA added to their existing therapy. Mean changes from baseline in weight after 52 weeks were as follows: liraglutide+AGI: –1.30 kg; liraglutide+GLN: –0.64 kg; liraglutide+metformin: –1.58 kg; liraglutide+pioglitazone: 0.18 kg. In addition, the differing changes from baseline in body weight depending on concomitant therapy in our study were consistent with results in previous global phase 3 studies of dulaglutide. For example, body weight reduction with DU 0.75 and metformin (–2.60 kg at week 52) [16] was greater than that observed with DU 0.75 monotherapy (–1.36 kg at week 26) [15].

This study was designed to detect adverse events occurring frequently during long-term treatment; thus, the sample size was not large enough to assess uncommon risks, including CV events and cancer. Due to the nature of the nonrandomized design of the study, the background and baseline characteristics of the patients in each combination therapy group differed. Also, because this was not a randomized study, comparisons of safety and efficacy results between the groups were not conducted, and estimates in each arm should not be interpreted comparatively. Finally, dulaglutide was

not studied in combination with DPP-4 inhibitors or sodium/glucose cotransporter 2 (SGLT2) inhibitors in this study.

In summary, once weekly dulaglutide 0.75 mg added onto monotherapy of SU, BG, AGI, TZD, or GLN in previously uncontrolled Japanese patients with T2D was overall well tolerated and improved glycemic control.

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Disclosure

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Author Contributions

M.E. and Y.T. were trial investigators and participated in data collection. M.T., T.I., A.O., and T.O. prepared the first draft of the manuscript. T.O. and A.O. were responsible for the statistical considerations in the analysis and trial design. M.T. and T.I. were responsible for trial design and for medical oversight during the trial. All authors participated in reviewing and interpreting the data and providing comments and revisions to the manuscript. All authors approved the final version of the manuscript and take full responsibility for the content.

Supplementary Table 1 Serious adverse events

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71
Large intestine polyp	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.4)
Acute myocardial infarction	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adenocarcinoma gastric	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina unstable	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Benign soft tissue neoplasm	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Bile duct cancer	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Bile duct stone	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Concussion	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery stenosis	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Gastric cancer	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischemia	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Edema	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian neoplasm[§]	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Pancreatic enzyme abnormality	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pelvic fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Pleurisy	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prostatitis[§§]	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)

The data are shown as numbers (%). AGI, α-glucosidase inhibitor; BG, biguanides; DU 0.75, 0.75 mg dulaglutide once weekly; GLN, glinides; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in full analysis set; SU, sulfonylurea; TZD, thiazolidinedione. MedDRA version 16.1. The cholangitis and bile duct cancer occurred in the same patient. [§]Denominator adjusted for gender-specific event for women: N=21 (DU 0.75 + SU), N=21 (DU 0.75 + BG), N=10 (DU 0.75 + AGI), N=14 (DU 0.75 + TZD), N=17 (DU 0.75 + GLN). [§§]Denominator adjusted for gender-specific event for men: N=95 (DU 0.75 + SU), N=40 (DU 0.75 + BG), N=55 (DU 0.75 + AGI), N=52 (DU 0.75 + TZD), N=54 (DU 0.75 + GLN).

Supplementary Table 2 Mean change from baseline (SE) 7-point SMBG profile parameters (mg/dL) at week 26 (LOCF) and week 52 (LOCF)

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71
Mean change from baseline (SE), Week 26 (LOCF)					
Mean of 7-point blood glucose	−56.81 (3.99)[**]	−42.41 (4.02)[**]	−62.61 (5.70)[**]	−58.28 (5.55)[**]	−60.19 (5.01)[**]
Mean of all pre-meals blood glucose	−46.07 (4.12)[**]	−28.83 (3.90)[**]	−53.34 (5.41)[**]	−43.91 (5.13)[**]	−50.47 (4.60)[**]
Mean of all PPBG	−66.55 (4.53)[**]	−53.89 (4.76)[**]	−71.06 (6.42)[**]	−70.30 (6.29)[**]	−68.49 (6.15)[**]
Breakfast 2-hour excursion	−25.42 (4.78)[**]	−29.66 (5.73)[**]	−27.48 (5.38)[**]	−30.11 (5.40)[**]	−19.39 (5.81)[**]
Lunch 2-hour excursion	−16.98 (4.95)[**]	−24.46 (6.90)[**]	−12.69 (6.15)[*]	−26.45 (6.37)[**]	−14.09 (7.38)
Dinner 2-hour excursion	−19.00 (5.77)[*]	−18.07 (7.28)[*]	−13.62 (5.85)[*]	−23.30 (8.47)[*]	−21.26 (6.99)[*]
All meals 2-hour excursion	−20.51 (3.08)[**]	−24.68 (3.91)[**]	−17.51 (3.90)[**]	−26.65 (3.98)[**]	−18.63 (3.74)[**]
Circadian variation[†]	−44.69 (4.15)[**]	−39.49 (5.12)[**]	−44.07 (4.63)[**]	−53.30 (5.80)[**]	−36.89 (6.19)[**]
Mean change from baseline (SE), Week 52 (LOCF)					
Mean of 7-point blood glucose	−51.12 (3.88)[**]	−44.78 (4.43)[**]	−60.39 (5.83)[**]	−59.89 (6.00)[**]	−60.32 (4.98)[**]
Mean of all pre-meals blood glucose	−43.86 (4.00)[**]	−31.87 (4.19)[**]	−52.52 (5.65)[**]	−44.16 (5.49)[**]	−51.57 (4.57)[**]
Mean of all PPBG	−58.32 (4.49)[**]	−55.39 (5.14)[**]	−66.94 (6.28)[**]	−72.92 (6.76)[**]	−67.84 (5.94)[**]
Breakfast 2-hour excursion	−16.29 (4.53)[**]	−26.68 (5.64)[**]	−28.02 (4.85)[**]	−27.36 (5.28)[**]	−26.45 (6.84)[**]
Lunch 2-hour excursion	−11.69 (5.53)[*]	−19.29 (5.83)[*]	−7.19 (5.83)	−30.35 (6.32)[**]	−9.14 (6.66)
Dinner 2-hour excursion	−14.78 (6.56)[*]	−22.97 (6.91)[*]	−8.52 (6.52)	−25.92 (7.86)[*]	−11.76 (5.63)[*]
All meals 2-hour excursion	−14.74 (3.32)[**]	−23.34 (3.68)[**]	−13.94 (3.17)[**]	−28.66 (3.79)[**]	−16.33 (3.37)[**]
Circadian variation[†]	−33.82 (4.40)[**]	−41.68 (5.33)[**]	−42.18 (4.06)[**]	−58.17 (6.30)[**]	−37.32 (6.08)[**]

AGI, α-glucosidase inhibitor; BG, biguanides; DU 0.75, 0.75 mg dulaglutide once weekly; GLN, glinides; LOCF, last observation carried forward; N, number of patients in full analysis set; PPBG, postprandial blood glucose; SU, sulfonylurea; TZD, thiazolidinedione. [†]The daily circadian variation was calculated as the difference between maximum and minimum (maximum − minimum) blood glucose values collected on a particular day. [**]denotes $p < 0.001$ for change from baseline within treatment group. [*]denotes $p < 0.05$ for change from baseline within treatment group.

Supplementary Table 3 Homeostasis Model Assessment at week 26 (LOCF) and week 52 (LOCF)

	DU 0.75 + SU N=131	DU 0.75 + BG N=61	DU 0.75 + AGI N=65	DU 0.75 + TZD N=66	DU 0.75 + GLN N=71
HOMA2-%B (insulin)					
Week 26 (LOCF)					
Mean (SE)	64.22 (3.18)	73.83 (4.40)	68.85 (3.74)	59.73 (3.48)	56.25 (3.64)
Mean change from baseline (SE)	29.10 (2.75)**	28.15 (2.79)**	30.88 (3.25)**	27.34 (2.60)**	26.93 (2.59)**
Week 52 (LOCF)					
Mean (SE)	61.04 (3.35)	71.63 (5.17)	66.04 (3.26)	57.90 (3.40)	61.63 (4.73)
Mean change from baseline (SE)	26.06 (2.77)**	26.05 (2.97)**	28.06 (3.61)**	25.38 (2.53)**	33.51 (3.81)**
HOMA2-%S (insulin)					
Week 26 (LOCF)					
Mean (SE)	90.61 (5.19)	85.34 (7.02)	97.98 (6.69)	107.06 (6.99)	96.10 (7.22)
Mean change from baseline (SE)	−4.80 (3.40)	−3.48 (4.39)	7.57 (5.60)	−5.50 (5.21)	−4.41 (4.05)
Week 52 (LOCF)					
Mean (SE)	90.13 (4.77)	86.13 (6.73)	96.71 (5.66)	112.57 (7.69)	98.50 (7.78)
Mean change from baseline (SE)	−3.99 (3.18)	−3.83 (4.89)	6.86 (5.24)	0.47 (5.87)	−5.51 (4.71)
HOMA2-%B (C-peptide)					
Week 26 (LOCF)					
Mean (SE)	80.49 (3.32)	85.77 (4.11)	86.44 (3.75)	73.08 (3.59)	67.35 (3.36)
Mean change from baseline (SE)	35.09 (2.91)**	32.20 (2.96)**	36.30 (3.25)**	29.55 (2.30)**	29.62 (2.59)**
Week 52 (LOCF)					
Mean (SE)	76.42 (3.61)	79.67 (4.33)	83.73 (3.65)	70.90 (3.49)	74.05 (4.76)
Mean change from baseline (SE)	31.03 (2.62)**	26.10 (2.63)**	33.60 (3.65)**	27.37 (2.29)**	36.32 (3.85)**
HOMA2-%S (C-peptide)					
Week 26 (LOCF)					
Mean (SE)	57.45 (2.77)	60.36 (3.98)	63.84 (3.28)	77.23 (5.14)	64.84 (4.13)
Mean change from baseline (SE)	−0.96 (1.97)	0.35 (2.50)	4.93 (2.59)	0.88 (3.93)	−3.10 (2.93)
Week 52 (LOCF)					
Mean (SE)	59.00 (2.66)	62.85 (3.49)	65.77 (3.50)	81.53 (5.54)	64.83 (3.94)
Mean change from baseline (SE)	0.59 (2.09)	2.84 (2.68)	6.86 (2.90)*	5.17 (3.55)	−3.11 (2.55)

AGI, α-glucosidase inhibitor; BG, biguanides; DU 0.75, 0.75 mg dulaglutide once weekly; GLN, glinides; HOMA2-%B, Updated Homeostasis Model Assessment of beta cell function; HOMA2-%S, Updated Homeostasis Model Assessment of insulin sensitivity; LOCF, last observation carried forward; N, number of patients in full analysis set; SU, sulfonylurea; TZD, thiazolidinedione. **denotes $p < 0.001$ for change from baseline within treatment group. *denotes $p < 0.05$ for change from baseline within treatment group.

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