ORIGINAL

Dose-ranging efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus

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Abstract. Sitagliptin is an oral, potent, highly selective, once-daily DPP-4 inhibitor indicated for the treatment of type 2 diabetes mellitus (T2DM). To assess the dose-ranging efficacy and safety/tolerability profile of once-daily sitagliptin 25, 50, 100, and 200 mg in Japanese patients with T2DM. In this randomized, double-blind, placebo-controlled study, 363 Japanese patients with inadequate glycemic control (HbA_{1c} = 6.5-10%; $FPG \leq 270$ mg/dL) were randomized (1:1:1:1) to placebo, sitagliptin 25, 50, 100, or 200 mg q.d. for 12 weeks. The primary endpoint was change from baseline in HbA_{1c} at Week 12. At Week 12, treatment with sitagliptin at all doses tested provided significant ($p < 0.001$) reductions in HbA_{1c} (-0.69 to -1.04%) from baseline (7.49 to 7.65%) relative to placebo. Sitagliptin significantly ($p < 0.001$) reduced fasting plasma glucose (FPG; -15.9 to -23.2 mg/dL) and 2-hour postprandial glucose (2-hr PPG; -40.3 to -65.0 mg/dL) relative to placebo, in a dose-dependent manner. At doses ≥ 50 mg, differences in HbA_{1c} , FPG, and 2-hr PPG between the sitagliptin groups were not statistically significant. Sitagliptin was generally well tolerated with a low and similar incidence of hypoglycemia and minimal weight gain relative to placebo. Treatment with sitagliptin for 12 weeks provided significant and clinically meaningful reductions in HbA_{1c} , FPG, and 2-hr PPG across the dose range studied and was generally well tolerated in Japanese patients with T2DM.

Key words: Glycemic control, DPP-4 inhibitor, MK-0431, Incretins

THE INCRETIN HORMONES glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released by the gastrointestinal tract in response to a meal [1, 2]. The intact forms of these peptides play an important role in regulating glucose homeostasis by stimulating both insulin production and glucose-dependent insulin secretion from pancreatic β -cells. GLP-1 further regulates plasma glucose levels by inhibiting glucagon secretion in a glucose-dependent manner, reducing food intake, and delaying gastric emptying. The actions of GLP-1 and

GIP *in vivo* are short-lived due to their rapid degradation and inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4) [3, 4].

Sitagliptin is an oral, potent, highly selective, once-daily DPP-4 inhibitor indicated for the treatment of type 2 diabetes mellitus (T2DM) [5]. Sitagliptin increases plasma levels of intact GLP-1 and GIP by two- to three-fold in patients with T2DM and in healthy volunteers [6-9]. In previously published studies conducted in non-Japanese patients with T2DM, treatment with sitagliptin was shown to reduce glycosylated he-

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moglobin (HbA_{1c}) as well as fasting and postprandial glucose levels in a dose-dependent manner [10, 11]. Sitagliptin is administered once daily as a single 100-mg tablet in non-Japanese patients with normal to mildly impaired renal function,[12] as this dosing regimen was considered optimally effective in large multinational clinical dose-range finding studies [10, 11, 13, 14]. Because sitagliptin is primarily renally excreted, sitagliptin dose adjustments to achieve plasma concentrations comparable to those in patients with normal renal function are recommended for patients with T2DM who have moderate renal insufficiency or severe renal insufficiency, including those with end-stage renal disease requiring dialysis [12, 15, 16].

In a recently published study, treatment with sitagliptin 100 mg q.d. for 12 weeks improved fasting and postprandial glycemic control and was generally well-tolerated in Japanese patients with T2DM [17]. We have previously reported that sitagliptin possesses similar pharmacokinetic and pharmacodynamic profiles in healthy Japanese and non-Japanese subjects [7, 8, 17]. The aim of the current study was to evaluate the glycemic efficacy, dose response, and safety/tolerability profile of sitagliptin 25, 50, 100, and 200 mg administered once daily for 12 weeks in a population of Japanese patients with T2DM.

Patients and Methods

Patients

Male and female Japanese patients aged 20 to 75 years with T2DM were eligible to participate if they had inadequate glycemic control and, at screening, were either taking an oral anti-hyperglycemic agent (OHA) or had not taken an OHA for at least 8 weeks. Patients with type 1 diabetes, history of diabetic ketoacidosis, serum C-peptide ≤ 0.7 ng/dL at screening, treatment with insulin, PPAR γ agonist (pioglitazone) or any combination OHA therapy in the 8 weeks prior to screening, unstable cardiac disease, active liver or gallbladder disease, inadequately controlled hypertension (systolic or diastolic blood pressure >160 mm Hg or >100 mm Hg, respectively), elevated serum creatinine (>1.3 mg/dL in men and >1.2 mg/dL in women), and elevations >2 -fold the upper limit of normal (ULN) in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were excluded. All patients provided written informed consent prior to the conduct of study procedures. The protocol

(Banyu Pharmaceutical Co., LTD. Protocol Number A202/Merck & Co., Inc. Protocol Number 044) was reviewed and approved by the appropriate committees and authorities at each study site and conducted in accordance with the Declaration of Helsinki. This study was performed between the dates of July 11, 2005 and March 8, 2006.

Study Design

This Phase II, randomized, double-blind, placebo-controlled, parallel-arm study (www.clinicaltrials.gov registry number: NCT00127192) was conducted at 97 sites in Japan. At screening/Visit 1, the HbA_{1c} inclusion criteria ranged from $\geq 6.5\%$ to $<10\%$ for patients not on an OHA (for at least 8 weeks) and $\geq 6\%$ to $\leq 9\%$ for patients on OHA monotherapy (within 8 weeks prior to Visit 1). The study included a screening diet/exercise run-in period of up to 8 weeks, including a 2-week single-blind placebo run-in period. At Visit 2, patients who had been on a diet and exercise program for at least 6 weeks and who had not taken an OHA for at least 6 weeks were eligible to directly enter the placebo run-in period. All other patients underwent a 6-week diet and exercise program (and wash-off period for patients on OHA at screening) prior to entering the placebo run-in period. This design ensured that patients received ≥ 8 weeks of diet and exercise therapy without OHA treatment before randomization.

Patients with an HbA_{1c} ≥ 6.5 and $<10\%$ and a fasting plasma glucose (FPG) ≤ 270 mg/dL upon entering the placebo run-in period and with $\geq 75\%$ compliance with the single-blind placebo were randomized (1:1:1:1:1) to double-blind treatment with placebo or with sitagliptin 25 mg, 50 mg, 100 mg, or 200 mg administered once daily before breakfast for 12 weeks. Patients were allocated to treatment assignment using an allocation schedule created by a Japanese third-party vendor that packaged the clinical supplies and provided them to the clinical site. Numbered containers were used to implement allocation and each patient was assigned the next number in the sequence upon being enrolled. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers only after case report forms were completed, the database was locked, and statistical analysis plans were finalized. During the double-blind active treatment phase, patients received

diet and exercise therapy. A follow-up phone call was made 14 days after the final dose of study medication to query patients regarding potential adverse experiences (AEs).

Endpoints

After an overnight fast, blood was collected for the assessment of HbA_{1c}, FPG, 1,5-anhydroglucitol (1,5-AG), and glycosylated albumin (GA) at baseline (i.e., Week 0 prior to the first dose of study medication) and at various time points throughout the study. Homeostasis model assessment- β cell (HOMA- β) was calculated to estimate pancreatic β -cell function. All patients were administered a standard meal tolerance test (MTT) at baseline and at Week 12. Patients took study medication 30 minutes prior to the standard meal, which was ingested within 15 minutes and contained 500 kcal: 60% from carbohydrate, 15% from protein, and 25% from fat. Plasma glucose, insulin, and C-peptide concentrations were measured at 0, 30, 60, and 120 minutes from the start of the meal for determination of 2-hour PPG, area under the glucose concentration-time curve (AUC), insulin AUC, and C-peptide AUC. The insulinogenic index was measured by calculating the ratio of the change in postprandial insulin/glucose from baseline to 30 minutes [17]. Plasma glucagon levels were measured at 0, 30, 60, and 120 minutes during the MTT in a subset of patients enrolled at clinic sites that were equipped to adequately collect and process the samples.

Safety and tolerability were evaluated from AE reports, vital signs (blood pressure, pulse rate and body weight), 12-lead electrocardiograms (ECGs), and laboratory tests, including hematology, blood chemistry, and urinalysis. AEs were rated by the investigators for the intensity and the potential relationship (definitely not, probably not, possibly, probably, or definitely) to study drug. AEs of special interest included hypoglycemia and selected gastrointestinal-related AEs (i.e., nausea, vomiting, and diarrhea). Patients were counseled to record results of self-monitored blood glucose levels and symptoms of hypoglycemia (e.g., sweating, anxiety, palpitations, headache, blurred vision, clouding of consciousness in diaries) for proper assessment of hypoglycemic events during the study. Hypoglycemia was assessed by the study site investigators through reviewing patient self-reports of signs and symptoms of hypoglycemia. A fingerstick blood glucose determination concurrent with the episode

was not required to assess an episode as hypoglycemia, although investigators could include the fingerstick glucose measurement, if it was available, in their assessment of the episode.

All efficacy and safety laboratory measurements were assayed at a central laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories [Mitsubishi Chemical Medience Corporation], Tokyo) by technicians blinded to treatment allocation.

Statistical Analyses

Efficacy analyses were performed on the full analysis set (FAS) consisting of all randomized patients who received at least one dose of study drug and who had valid measurements both at baseline and at least one post-treatment measurement. The primary efficacy endpoint, the change from baseline in HbA_{1c} at Week 12, was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, prior OHA use, and baseline HbA_{1c} value as covariates. The between-group differences (relative to placebo) and associated 95% confidence intervals (CIs) for efficacy endpoints were assessed by testing the differences in the least squares (LS) mean changes from baseline at Week 12. Missing data were handled using the last observation carried forward method. An alpha level of ≤ 0.050 (two sided) was considered statistically significant. A stepwise linear contrast test based on the ANCOVA model was used to examine the dose-response relationship for placebo and the sitagliptin 25-, 50-, 100-, and 200-mg groups. LS mean differences between groups (relative to placebo) and associated 95% CI for each of the subgroups were estimated based on the aforementioned ANCOVA model to evaluate the consistency of the HbA_{1c}-lowering effect of sitagliptin relative to placebo across predefined subgroups including baseline HbA_{1c} stratum ($\leq 8.0\%$ or $> 8.0\%$).

Safety analyses were performed on the all-patients-as-treated population (APaT) consisting of all patients who took at least one dose of study drug. Summary statistics for changes from baseline in safety continuous parameters were calculated. For overall AEs, drug-related AEs, hypoglycemia, and selected gastrointestinal-related AEs (i.e., nausea, vomiting, and diarrhea), the comparisons with placebo were conducted by Fisher's exact test, and between-group differences (relative to placebo) and associated 95% CIs were reported.

Fig. 1. Disposition of screened/ randomized patients

Table 1. Summary of patient demographics and baseline characteristics

Parameter	Placebo	Sitagliptin			
	n=73	25 mg q.d. n=80	50 mg q.d. n=72	100 mg q.d. n=70	200 mg q.d. n=68
Age, yr	60.2 ± 8.0	59.9 ± 7.9	60.2 ± 9.4	58.3 ± 9.5	60.6 ± 7.7
Gender, n (%)					
Women	23 (31.5)	29 (36.3)	25 (34.7)	34 (48.6)	28 (41.2)
Men	50 (68.5)	51 (63.8)	47 (65.3)	36 (51.4)	40 (58.8)
BMI, kg/m ²	24.1 ± 3.2	25.0 ± 3.6	24.5 ± 3.6	24.2 ± 2.8	24.4 ± 3.0
Duration of diabetes, yr	6.4 ± 5.5	4.7 ± 4.3	5.6 ± 6.4	5.4 ± 5.4	5.1 ± 4.9
Prior use of OHAs, n (%)					
Absence	29 (39.7)	37 (46.3)	34 (47.2)	41 (58.6)	35 (51.5)
Presence	44 (60.3)	43 (53.8)	38 (52.8)	29 (41.4)	33 (48.5)
HbA _{1c} , %	7.74 ± 0.93	7.49 ± 0.82	7.57 ± 0.84	7.56 ± 0.80	7.65 ± 0.82
FPG, mg/dL	156.48 ± 35.11	145.71 ± 37.58	144.25 ± 28.96	142.60 ± 31.77	148.40 ± 33.35

Data are expressed as mean ± standard deviation or frequency unless otherwise noted.

BMI = body mass index; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; OHA = oral antihyperglycemic agents; q.d. = once daily

Results

Of 473 patients screened for participation in this study, 110 were not randomized because they did not meet inclusion or met exclusion criteria (n=85), withdrew consent (n=20), or other reason (n=5). A total of 363 patients were randomized to receive double-blind treatment with once-daily placebo (n=73), sitagliptin 25 mg (n=80), 50 mg (n=72), 100 mg (n=70), or 200 mg (n=68) for 12 weeks (Figure 1). Overall, 351 (97%) patients completed the study, and 12 pa-

tients discontinued before study completion. The discontinuation rate was somewhat higher in the placebo group relative to the sitagliptin groups, with withdrawal of consent and lack of efficacy being the most common reasons for discontinuation. All randomized patients contributed to the efficacy and safety analyses. Baseline demographics were generally well matched, and baseline glycemic characteristics were similar across the treatment groups (Table 1). Patients randomized in this study had a mean baseline HbA_{1c} of 7.60% and FPG of 147.5 mg/dL. The mean duration of diabetes was 5.4 years, and 51.5% of pa-

Fig. 2. Least squares mean change from baseline ($\pm$ SE) in HbA_{1c} over a 12-week treatment period.

tients had received prior OHA therapy within 8 weeks before initiation of the screening period.

Efficacy

At Week 12, all doses of sitagliptin produced significant reductions from baseline in HbA_{1c} ($p < 0.001$) (Table 2). A significant dose-response relationship (as assessed by stepwise linear contrast test) in HbA_{1c} lowering was observed across all of the sitagliptin doses tested and placebo ($p < 0.001$ for all doses). Similar magnitude reductions from baseline in HbA_{1c} were seen across sitagliptin doses ranging from 50 mg to 200 mg, with the 50-mg group, producing a placebo-subtracted change from baseline of 0.99% (95% CI: -1.16, -0.82). No significant between-group differences in HbA_{1c} were seen for the 50-, 100-, and 200-mg doses of sitagliptin. The 25-mg dose produced significantly smaller reductions in HbA_{1c} compared with the other doses ($p < 0.001$ vs. sitagliptin 25 mg for all pair-wise comparisons). Over time, the placebo group showed a slow progressive increase from baseline in HbA_{1c} out to Week 12 (Figure 2). For the sitagliptin 25-mg group, maximum reductions from baseline in HbA_{1c} were reached by Week 8 and appeared stable out to Week 12. In contrast, the other sitagliptin groups showed a progressive reduction from baseline in HbA_{1c} out to Week 12 with no apparent plateau in the response. In the subgroup of patients with baseline HbA_{1c} $\leq 8\%$, sitagliptin doses of 50 mg, 100 mg, and 200 mg showed similar placebo-subtracted reductions from baseline in HbA_{1c} of -0.76% (95% CI: -0.93, -0.58), -0.80% (95% CI: -0.98, -0.63), and -0.76%

(95% CI: -0.94, -0.59), respectively. In the subgroup of patients with baseline HbA_{1c} $> 8\%$, treatment with sitagliptin 200 mg produced the numerically largest placebo-subtracted reductions from baseline in HbA_{1c} of -1.59% (95% CI: -1.97, -1.21), with substantial reductions of -1.38% (95% CI: -1.78, -0.99) in the 50-mg group and -1.31% (95% CI: -1.72, -0.89) in the 100-mg group.

Significant dose-dependent reductions from baseline in FPG were observed across the sitagliptin doses compared with placebo ($p < 0.001$ for all doses) (Table 2; Figure 3). The reductions observed at doses of 100 and 200 mg were numerically but not statistically superior to 50 mg. The only pairwise comparison that reached statistical significance was between the 25-mg and 200-mg groups ($p < 0.050$). Compared with placebo, sitagliptin also led to significant ($p < 0.001$ for all doses of sitagliptin) dose-related increases from baseline in 1,5-AG and significant ($p < 0.001$ for all doses of sitagliptin) dose-related reductions from baseline in GA (Table 2).

Relative to placebo, all doses of sitagliptin produced significant dose-related increases from baseline in HOMA- β ($p < 0.050$ vs. placebo for all doses) (Table 2). There were no significant differences in the HOMA- β response among the 25-, 50-, 100-, and 200-mg doses, except for a significant difference observed when the 25-mg group was compared with the 100-mg group ($p = 0.030$).

With respect to the MTT parameters, treatment with sitagliptin across all doses tested led to significant reductions from baseline in 2-hr PPG and glucose AUC_{0-2 hr} relative to placebo at Week 12 ($p < 0.001$ vs. placebo for all doses), with the 200-mg group providing the largest magnitude changes from baseline in both parameters (Table 2). No significant between-group differences in 2-hr PPG were seen between the sitagliptin 25- and 50-mg doses or among sitagliptin doses of 50, 100, and 200 mg. In contrast, the 25-mg dose produced significantly smaller reductions in 2-hr PPG compared with the 100-mg ($p = 0.010$) and 200-mg doses ($p < 0.001$) (data not shown). No significant between-group differences in glucose prior to AUC_{0-2 hr} were seen between sitagliptin doses of 50 and 100 mg or between sitagliptin doses of 100 and 200 mg; however, significantly smaller reductions in glucose AUC_{0-2 hr} were observed with sitagliptin 25 mg compared with sitagliptin 50 mg, 100 mg, and 200 mg ($p = 0.026$, $p = 0.004$ and $p < 0.001$, respec-

Table 2. Baseline, Week 12, and change from baseline in fasting and postprandial glycemic endpoints

Parameter	Placebo	Sitagliptin			
		25 mg q.d.	50 mg q.d.	100 mg q.d.	200 mg q.d.
Fasting Glycemic Endpoints					
HbA_{1c} (%)					
n	73	80	72	70	68
Baseline ^a	7.74 (0.93)	7.49 (0.82)	7.57 (0.84)	7.56 (0.80)	7.65 (0.82)
Week 12 ^a	8.04 (1.24)	7.11 (0.94)	6.87 (0.82)	6.85 (0.90)	6.88 (0.80)
Change from baseline ^b	0.28 (0.16, 0.40)**	-0.41 (-0.52, -0.29)**	-0.71 (-0.83, -0.59)**	-0.69 (-0.81, -0.56)**	-0.76 (-0.89, -0.64)**
Change from placebo ^c	--	-0.69 (-0.85, -0.52) ^{††}	-0.99 (-1.16, -0.82) ^{††}	-0.96 (-1.14, -0.79) ^{††}	-1.04 (-1.21, -0.86) ^{††}
Fasting Plasma Glucose (mg/dL)					
n	73	80	72	70	68
Baseline ^a	156.5 (35.1)	145.7 (37.6)	144.3 (29.0)	142.6 (31.8)	148.4 (33.3)
Week 12 ^a	159.5 (33.2)	136.9 (27.0)	134.3 (30.0)	129.7 (26.9)	131.1 (25.1)
Change from baseline ^b	6.3 (1.7, 10.9)*	-9.6 (-14.0, -5.3)**	-11.4 (-16.0, -6.8)**	-14.6 (-19.2, -9.9)**	-16.9 (-21.6, -12.1)**
Change from placebo ^c	--	-15.9 (-22.3, -9.6) ^{††}	-17.7 (-24.2, -11.2) ^{††}	-20.8 (-27.4, -14.3) ^{††}	-23.2 (-29.8, -16.6) ^{††}
1,5-Anhydroglucitol (μg/mL)					
n	73	80	72	70	68
Baseline ^a	4.83 (3.48)	5.99 (3.75)	6.79 (4.53)	6.59 (4.36)	6.23 (4.92)
Week 12 ^a	4.39 (2.95)	8.79 (5.43)	10.83 (5.91)	10.56 (5.87)	10.93 (7.09)
Change from baseline ^b	-0.25 (-0.93, 0.43)	2.82 (2.18, 3.47)**	3.96 (3.28, 4.64)**	3.88 (3.19, 4.56)**	4.67 (3.97, 5.36)**
Change from placebo ^c	--	3.07 (2.14, 4.00) ^{††}	4.21 (3.25, 5.17) ^{††}	4.12 (3.15, 5.09) ^{††}	4.92 (3.95, 5.89) ^{††}
Glycosylated Albumin (%)					
n	73	80	72	70	68
Baseline ^a	23.7 (4.5)	21.5 (3.9)	22.0 (4.2)	21.9 (4.5)	21.9 (3.9)
Week 12 ^a	24.2 (4.9)	19.7 (3.7)	19.4 (4.1)	19.3 (4.4)	19.0 (3.0)
Change from baseline ^b	0.7 (0.2, 1.1)*	-1.9 (-2.4, -1.5)**	-2.6 (-3.1, -2.2)**	-2.6 (-3.0, -2.1)**	-2.9 (-3.4, -2.5)**
Change from placebo ^c	--	-2.6 (-3.2, -2.0) ^{††}	-3.3 (-3.9, -2.7) ^{††}	-3.2 (-3.9, -2.6) ^{††}	-3.6 (-4.3, -3.0) ^{††}
HOMA-β (%)					
n	71	80	72	70	68
Baseline ^a	26.4 (17.3)	37.0 (27.8)	33.5 (29.9)	37.8 (39.7)	32.0 (18.7)
Week 12 ^a	28.0 (19.2)	45.6 (34.4)	43.5 (31.9)	52.5 (54.8)	42.6 (23.5)
Change from baseline ^b	2.5 (-1.4, 6.4)	8.3 (4.7, 11.9)**	10.0 (6.2, 13.8)**	14.1 (10.2, 18.0)**	10.8 (6.9, 14.7)**
Change from placebo ^c	--	5.8 (0.5, 11.1) [†]	7.5 (2.1, 13.0) [†]	11.6 (6.1, 17.1) ^{††}	8.3 (2.8, 13.8) [†]
Postprandial Glycemic Endpoints					
PP Glucose (120 min); mg/dL					
n	67	77	70	68	67
Baseline ^a	249.7 (66.6)	230.7 (57.5)	244.3 (63.9)	235.1 (64.6)	244.7 (71.9)
Week 12 ^a	248.9 (70.8)	195.5 (54.5)	192.8 (60.4)	179.7 (59.0)	180.0 (59.9)
Change from baseline ^b	1.7 (-8.3, 11.7)	-38.6 (-47.9, -29.3)**	-50.5 (-60.2, -40.7)**	-56.6 (-66.5, -46.7)**	-63.4 (-73.3, -53.4)**
Change from placebo ^d	--	-40.3 (-53.9, -26.6) ^{††}	-52.2 (-66.1, -38.2) ^{††}	-58.3 (-72.4, -44.2) ^{††}	-65.0 (-79.1, -51.0) ^{††}
PP Glucose AUC_{0-2h}; mg•h/dL					
n	67	77	69	68	67
Baseline ^a	472.1 (90.9)	440.7 (81.9)	457.7 (89.2)	448.9 (92.5)	466.9 (102.0)
Week 12 ^a	477.0 (99.0)	393.3 (76.9)	381.4 (91.5)	367.5 (84.0)	366.3 (76.8)
Change from baseline ^b	9.6 (-5.2, 24.3)	-53.5 (-67.3, -39.7)**	-76.2 (-90.7, -61.7)**	-83.2 (-97.8, -68.5)**	-96.9 (-111.6, -82.2)**
Change from placebo ^d	--	-63.1 (-83.3, -42.9) ^{††}	-85.8 (-106.4, -65.1) ^{††}	-92.7 (-113.6, -71.9) ^{††}	-106.5 (-127.2, -85.7) ^{††}
PP Insulin AUC_{0-2h}; μU•h/mL					
n	67	77	70	68	67
Baseline ^a	55.8 (27.1)	81.7 (55.0)	72.0 (49.9)	82.5 (62.6)	76.5 (45.8)
Week 12 ^a	58.9 (31.8)	87.1 (64.5)	74.9 (52.1)	89.3 (53.7)	87.2 (41.5)
Change from baseline ^b	0.1 (-6.9, 7.1)	6.7 (0.2, 13.2)*	2.6 (-4.2, 9.4)	8.2 (1.3, 15.1)*	11.1 (4.1, 18.0)*
Change from placebo ^d	--	6.6 (-3.0, 16.3)	2.5 (-7.2, 12.3)	8.1 (-1.9, 18.1)	11.0 (1.1, 20.9) [†]
PP C-peptide AUC_{0-2h}; ng•h/mL					
n	67	77	70	68	67
Baseline ^a	8.49 (2.49)	10.02 (3.27)	9.43 (3.25)	9.68 (3.04)	9.72 (2.62)
Week 12 ^a	8.40 (2.61)	10.12 (3.44)	9.38 (3.19)	9.95 (2.86)	10.77 (2.67)
Change from baseline ^b	-0.25 (-0.66, 0.16)	0.19 (-0.19, 0.57)	-0.05 (-0.45, 0.34)	0.29 (-0.11, 0.70)	1.09 (0.68, 1.49)**
Change from placebo ^d	--	0.44 (-0.12, 1.00)	0.19 (-0.38, 0.76)	0.54 (-0.04, 1.12)	1.34 (0.76, 1.91) ^{††}
Insulinogenic Index					
n	67	77	69	68	67
Baseline ^a	0.25 (0.21)	0.35 (0.28)	0.26 (0.33)	0.33 (0.27)	0.30 (0.20)
Week 12 ^a	0.25 (0.17)	0.46 (0.45)	0.44 (0.46)	0.65 (1.42)	0.56 (0.39)
Change from baseline ^b	-0.00 (-0.16, 0.16)	0.12 (-0.03, 0.27)	0.18 (0.03, 0.34)*	0.32 (0.16, 0.48)**	0.26 (0.10, 0.42)*
Change from placebo ^d	--	0.12 (-0.10, 0.34)	0.19 (-0.04, 0.41)	0.32 (0.09, 0.55) [†]	0.26 (0.04, 0.49) [†]
PP Glucagon AUC_{0-2h}; pg•h/mL					
n	31	37	31	30	30
Baseline ^a	232.5 (53.6)	256.6 (79.9)	238.9 (75.6)	254.5 (77.6)	252.0 (82.0)
Week 12 ^a	235.1 (53.5)	236.7 (71.6)	213.1 (76.9)	226.1 (78.8)	241.8 (89.2)
Change from baseline ^b	0.1 (-14.0, 14.1)	-17.3 (-30.1, -4.4)*	-27.4 (-41.4, -13.4)**	-23.7 (-38.1, -9.2)*	-8.9 (-23.2, 5.3)
Change from placebo ^d	--	-17.3 (-36.4, 1.8)	-27.5 (-47.3, -7.6) [†]	-23.7 (-44.0, -3.5) [†]	-9.0 (-29.0, 11.1)

^aBaseline and Week 12 data are presented as mean (standard deviation); ^bChange from baseline = least squares mean change from baseline at Week 12 (95% confidence interval [CI]); ^cPlacebo-subtracted change from baseline at Week 12 (95% CI); ^dChange from placebo = between-treatment difference in least squares mean change from baseline at Week 12 (95% CI); ***p* < 0.001 vs. baseline; **p* < 0.05 vs. baseline; ^{††}*p* < 0.001 vs. placebo; [†]*p* < 0.05 vs. placebo; AUC_{0-2h} = area under the curve from 0 to 2 hours; PP= postprandial; q.d. = once daily

Fig. 3. Effect of sitagliptin on (a) fasting plasma glucose (PPG) and (b) 2-hr postprandial glucose (PPG) following 12 weeks of treatment. Results are presented as placebo-subtracted change from baseline.

tively) and with 50 mg compared with 200 mg ($p=0.049$) (data not shown). Of all the sitagliptin doses tested, only the 200-mg group produced significant increases from baseline in insulin $AUC_{0-2 \text{ hr}}$ ($p=0.030$) and C-peptide $AUC_{0-2 \text{ hr}}$ ($p<0.001$) compared with placebo. The insulinogenic index was significantly increased with sitagliptin 100 and 200 mg compared with placebo ($p<0.050$). The effects of sitagliptin on plasma glucagon levels were examined in a subset of patients enrolled at sites equipped to appropriately collect and process the samples. Although the predefined stepwise linear contrast test that included the 200-mg dose was not significant, treatment with sitagliptin 25, 50 and 100 mg led to significant ($p<0.001$ in 50 mg, $p<0.05$ in 25 and 100 mg) reductions from baseline in glucagon $AUC_{0-2 \text{ hr}}$. Significant reductions from baseline relative to placebo were observed for the 50- and 100-mg doses of sitagliptin ($p<0.05$).

Safety

Compared with the placebo group, the incidences of overall clinical AEs were similar in the 25-mg group, with a dose-related trend toward an increased incidence across the 50-, 100-, and 200-mg groups (Table 3). There were similar proportions of patients across the placebo, sitagliptin 25-, 50-, 100-, and 200-mg groups for whom infections and infestations disorder AEs were reported (20 [27.4%], 17 [21.3%], 22 [30.6%], 29 [41.4%], 18 [26.5%], respectively); there was no dose-dependent increase in the proportion of patients in these groups for whom gastrointestinal disorders AEs were reported (9 [12.3%], 13 [16.3%], 13 [18.1%], 9 [12.9%], 9 [13.2%], respectively), with similar incidences observed for the placebo, 100-, and 200-mg groups. The most commonly reported clinical AE was nasopharyngitis, which had a similar incidence across the placebo and sitagliptin groups (17 [23.3%], 16 [20.0%], 16 [22.2%], 23 [32.9%] and 12 [17.6%] for the placebo, sitagliptin 25-, 50-, 100-, and 200-mg groups, respectively). The incidences of hypoglycemia and selected gastrointestinal AEs across the sitagliptin groups were low and comparable to that seen in the placebo group (Table 3). Only one patient in this study (a patient in the 200-mg group) discontinued due to a clinical AE; a clinical AE of myocardial ischemia determined by the investigator to be “definitely not related” to study medication.

The incidences of drug-related clinical AEs were generally similar between the placebo and the individual sitagliptin groups, with no apparent dose-related trend (Table 3). There were no clinically meaningful differences in the incidences of specific drug-related clinical AEs across the groups (Table 3). No patients in this study discontinued due to drug-related clinical AEs (Table 3). There were 3 patients for whom 5 serious AEs were reported.

All serious AEs were determined by the investigator to be “definitely not related” to study medication: 1 patient in the 50-mg group (angina pectoris) and 2 patients in the 200-mg group (one patient had an overdose and 1 patient reported AEs of cardiac failure, hypertensive heart disease, and myocardial ischemia). Per protocol, overdose was defined as a serious AE, regardless of whether an adverse event was associated with the overdose. The patient for whom an AE of overdose was reported took sitagliptin 400 mg/day for one day without any associated adverse signs or symptoms. No patients discontinued due to serious clinical AEs.

Table 3. Summary of adverse events

Adverse events	Number (%) of patients				
	Placebo n=73	Sitagliptin			
		25 mg q.d. n=80	50 mg q.d. n=72	100 mg q.d. n=70	200 mg q.d. n=68
One or more clinical AEs	39 (53.4)	46 (57.5)	47 (65.3)	46 (65.7)	50 (73.5)
Serious clinical AEs	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	2 (2.9)
Drug-related clinical SAEs ^a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to clinical AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Discontinued due to drug-related clinical AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to clinical SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical AEs of interest					
Hypoglycemia	2 (2.7)	1 (1.3)	3 (4.2)	3 (4.3)	3 (4.4)
Gastrointestinal AEs ^b	1 (1.4)	3 (3.8)	0 (0.0)	0 (0.0)	3 (4.4)
Clinical drug related adverse events ^a	3 (4.1)	6 (7.5)	3 (4.2)	5 (7.1)	1 (1.5)
Anemia	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Bundle branch block right ^c	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations ^c	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal polyp	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
ECG T wave amplitude decreased	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
ECG T wave inversion	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoglycemia	1 (1.4)	0 (0.0)	1 (1.4)	3 (4.3)	1 (1.5)
Dizziness postural	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Neuropathy peripheral	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Epistaxis	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
One or more laboratory AEs	8 (11.0)	15 (18.8)	14 (19.4)	12 (17.1)	8 (11.8)
Drug-related laboratory AEs	2 (2.7)	3 (3.8)	6 (8.3)	1 (1.4)	2 (2.9)
Serious laboratory AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to laboratory AEs	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)
Discontinued due to drug-related laboratory AEs	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)

^aDetermined by the investigator to be possibly, probably, or definitely drug-related; ^bRedefined category includes gastrointestinal AEs of nausea, vomiting, and diarrhea; ^cOne patient in the 25-mg group experienced two drug-related clinical adverse experiences of “bundle branch block right” and “palpitations” during the 12-week study. This patient was counted once in the overall tally of total drug-related clinical adverse experiences; AE= adverse event; ECG = electrocardiogram; q.d. = once daily; SAE= serious adverse event

There was no dose-dependent increase in the proportion of patients in these groups for whom laboratory AEs were reported (8 (11.0%), 15 (18.8%), 14 (19.4%), 12 (17.1%), and 8 (11.8%) in the placebo, sitagliptin 25-, 50-, 100-, and 200-mg groups, respectively (Table 3), with similar incidences observed for the placebo and 200-mg groups. Among the specific laboratory AEs, a total of 4 patients in the 50-mg group experienced elevations in ALT (4 [5.6%]) and AST (3 [4.2%]) versus none in the higher-dose groups. There was a higher incidence of creatine kinase elevations in the 25-mg group (7 [8.8%]) compared with the other treatment groups (2 [2.7%], 2 [2.8%], 1 [1.4%], and 1 [1.5%] for placebo, sitagliptin

50 mg, 100 mg, and 200 mg, respectively). Two (2.5%), 3 (4.3%), and 3 (4.4%) of patients in the sitagliptin 25-, 100-, and 200-mg groups were reported to have an AE of proteinuria compared with none in the placebo and sitagliptin 50-mg groups. There was no evidence of a dose-related trend toward increased incidences of laboratory AEs across the sitagliptin groups. The incidences of drug-related laboratory AEs were low and generally similar across the placebo, sitagliptin 25-, 100-, and 200-mg groups (2 [2.7%], 3 [3.8%], 1 [1.4%] and 2 [2.9%], respectively), with a slightly higher rate in the 50 mg group (6 [8.3%]). All laboratory AEs resolved spontaneously without any medical intervention; 2 patients discontinued study medication

prematurely due to laboratory AEs.

At Week 12, treatment with sitagliptin had no clinically meaningful effect on body weight relative to baseline or placebo. The placebo group showed a small non-significant reduction from baseline in body weight of -0.5 kg (95% CI: -0.8, -0.1; $p=0.005$), whereas slight increases of 0.4 kg (95% CI: 0.1, 0.7; $p<0.050$), 0.3 kg (95% CI: 0.0, 0.6; $p<0.050$), 0.1 kg (95% CI: -0.2, 0.5; $p=0.386$), and 0.3 kg (95% CI: 0.0, 0.6; $p=0.079$) were observed across the sitagliptin 25-, 50-, 100-, and 200-mg groups, respectively. The changes in body weight observed with sitagliptin treatment did not appear to be dose related. No clinically meaningful mean changes from baseline in vital signs were observed in any treatment group.

Discussion

This 12-week, placebo-controlled, randomized study evaluated the glycemic efficacy, dose-response and safety/tolerability profile of sitagliptin doses ranging from 25 to 200 mg q.d. in Japanese patients with T2DM who had inadequate glycemic control with diet and exercise therapy alone. Treatment with sitagliptin monotherapy led to significant dose-related and clinically meaningful reductions in HbA_{1c} relative to placebo after 12 weeks of treatment. The 50-mg dose of sitagliptin was maximally effective at reducing HbA_{1c}, with similar magnitude reductions observed in the 100-mg group and only small numerically greater reductions in the 200-mg group. This finding suggests that, in Japanese patients with T2DM, starting treatment with the 100- and 200-mg doses of sitagliptin does not provide further, clinically meaningful improvements in HbA_{1c} beyond that seen with the 50-mg dose in this treatment period. The improvements in HbA_{1c} observed in this study of Japanese patients with T2DM were maintained over the 12-week treatment period for all sitagliptin doses, whereas deterioration was observed in the placebo group. A previous, longer-term study conducted in non-Japanese patients with T2DM demonstrated that sitagliptin doses of 100 and 200 mg produced maximum reductions in HbA_{1c} by Week 12 with no further improvements observed out to week 18 [14].

In addition to reductions in HbA_{1c}, treatment with sitagliptin also provided significant dose-dependent improvements in other important glycemic endpoints compared with placebo, including FPG, 2-hr

PPG, glucose AUC_{0-2hr}, 1,5-AG, and GA. For FPG, 2-hr PPG, and glucose AUC_{0-2hr}, stepwise numerically greater improvements were observed across the entire dose range, suggesting that some patients in this population may receive additional benefit from a higher dose of sitagliptin. The 50-mg dose produced significantly greater improvements in 1,5-AG and GA relative to the 25-mg dose, with no further improvements observed at doses of 100 and 200 mg. The combined improvements in FPG, 2-hr PPG and glucose AUC_{0-2hr} observed in this study of Japanese patients demonstrates that sitagliptin provides clinically meaningful glucose-lowering efficacy in both the fasting and postprandial states.

All sitagliptin doses provided numerical increases relative to placebo in insulin AUC_{0-2hr}, although statistical significance was reached at the 200-mg dose only. The effects of sitagliptin therapy on plasma insulin levels in the context of lowered glucose excursion suggest that sitagliptin may enhance the insulin response following a meal. Significant improvements in β -cell function were observed with all sitagliptin doses relative to placebo using both fasting and postprandial measurements (i.e., HOMA- β and insulinogenic index). This study also assessed the effects of sitagliptin on plasma glucagon levels in a subset of patients enrolled at clinic sites equipped to adequately collect and process the samples for this assay. Treatment with sitagliptin 25, 50, or 100 mg led to significant reductions from baseline in glucagon AUC_{0-2hr}, although there was no evidence of a dose-related trend in the glucagon response. Significant reductions from baseline in glucagon AUC_{0-2hr} were also observed with sitagliptin 50 and 100 mg relative to placebo. Consistent with the glucagon-lowering previously reported by Herman *et al.* [5], this finding suggests that sitagliptin alters the secretion of glucagon by the α -cell, although further research may better elucidate the effects of sitagliptin on hepatic glucose output. Consistent with prior findings in non-Japanese patients, there was no significant effect of sitagliptin treatment compared with placebo on HOMA-IR in the current study (data not shown), suggesting that sitagliptin does not affect peripheral insulin sensitivity [10, 11, 13, 14].

In this study, there were numerical incremental improvements in both FPG and 2-hr PPG with sitagliptin doses of 100 (N=70) and 200 mg (N=68) relative to the 50-mg dose (N=72); however, the differences ob-

served between these treatment groups were not statistically significant. Collectively, these observations suggest that the 50-mg dose provided near maximal fasting and postprandial glycemic efficacy in Japanese patients, thus supporting sitagliptin 50 mg as the primary dose in the Phase III development program in Japan. Since numerically larger reductions in both FPG and 2-hr PPG were seen in this study with increasing doses of sitagliptin, further investigation is warranted to determine the possible increased glycemic efficacy of sitagliptin doses greater than 50 mg in Japanese patients with T2DM. The results of the present study in Japanese patients with T2DM are consistent with those observed in previous monotherapy studies conducted in non-Japanese patients with T2DM that demonstrated some improvement in glycemic parameters with 100 mg compared with 50 mg of sitagliptin [10, 11].

Sitagliptin was generally well-tolerated in this study of Japanese patients with T2DM. Although the overall AE rate was somewhat higher in the sitagliptin treatment groups compared with placebo, drug-related AEs and discontinuations due to drug-related AEs occurred at a low and generally similar rate across treatment groups. A very low incidence of hypoglycemia was observed with sitagliptin treatment despite the effective fasting and postprandial glucose control seen in this study. The incidence of hypoglycemia observed in the sitagliptin groups did not appear to be meaningfully different from that seen in the

placebo group. This finding is consistent with evidence indicating that GLP-1 stimulates insulin release in a glucose-dependent manner [18]. The incidence of gastrointestinal AEs was evaluated in this study since sitagliptin increases the level of active GLP-1 in the plasma and GLP-1 analogues are known to be associated with symptoms of nausea, vomiting, and diarrhea [19]. In this study, the incidence of gastrointestinal AEs was very low with no clinically meaningful differences between the sitagliptin and placebo groups. Finally, treatment with sitagliptin had a generally neutral effect on body weight without evidence of a dose-related increase. In conclusion, this 12-week study in Japanese patients with T2DM and inadequate glycemic control on diet and exercise therapy alone demonstrated that once-daily sitagliptin at doses of 25, 50, 100, and 200 mg provided statistically significant and clinically important reductions in HbA_{1c}, FPG, and 2-hr PPG as well as significant improvements in indices of insulin secretion and β -cell function, including HOMA- β and insulinogenic index. Treatment with sitagliptin was well tolerated and was associated with a low rate of hypoglycemia as well as a neutral effect on body weight.

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Appendix

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