Randomized, Double-Blind, Dose-Ranging Study of TAK-875, a Novel GPR40 Agonist, in Japanese Patients With Inadequately Controlled Type 2 Diabetes

Kohei Kaku, md, phd[1]
Takahiro Araki, md[2]
Ryoji Yoshinaka, beng[2]

OBJECTIVE—Assessment of the efficacy and safety of TAK-875 (a novel GPR40 agonist) in Japanese patients with type 2 diabetes inadequately controlled by diet/exercise.

RESEARCH DESIGN AND METHODS—This was a phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week dose-ranging evaluation of TAK-875 (6.25–200 mg once daily) with the primary end point of change in A1C at week 12. A nonblinded group received 1 mg glimepiride once daily as an active control.

RESULTS—A total of 396 patients were randomized to receive TAK-875 (n = 299), placebo (n = 48), or glimepiride (n = 49). The least square mean changes in A1C at week 12 from baseline were as follows: 0.09% in the placebo group; −0.54, −0.67, −0.88, −1.27, −1.29, and −1.40% in the 6.25-, 12.5-, 25-, 50-, 100-, and 200-mg TAK-875 groups, respectively; and −1.32% in the 1-mg glimepiride group. All TAK-875 groups had statistically significant reductions in A1C compared with placebo ($P < 0.0001$), and those receiving ≥50 mg TAK-875 achieved reductions in A1C equivalent to those with glimepiride. Results for other glycemic parameters, including improvements during a meal tolerance test, mirrored these positive findings with TAK-875. There were no significant differences in incidence of adverse events among the groups and no dose-dependent changes in tolerability. Hypoglycemic episodes were reported in 0.7% of patients in the TAK-875 groups and in 4.1% of the glimepiride group.

CONCLUSIONS—TAK-875 produced clinically and statistically significant improvements in glycemic control in patients with type 2 diabetes inadequately controlled by diet and exercise, and it was well tolerated with a lower propensity to cause hypoglycemia.

Diabetes Care 36:245–250, 2013

Free fatty acids (FFAs) are not only an important nutritional source—they also act as signaling molecules for a number of cellular processes including insulin secretion (1). There is accumulating evidence that long-chain fatty acids amplify glucose-stimulated insulin secretion from pancreatic β cells, and this effect is mediated through activation of the G-protein–coupled receptor (GPR)40, also known as free fatty acid receptor 1 (2). GPR40, as a potential target for the treatment of diabetes, is receiving much attention, since it is highly expressed in pancreatic β cells (3–5).

TAK-875 is an orally bioavailable GPR40 agonist that was chosen as a lead compound for clinical evaluation (6). An initial clinical study of single oral doses of 25–800 mg TAK-875 in healthy volunteers in the U.S. showed no glucose-lowering effects or dose-dependent safety/tolerability changes (7). The authors concluded that these pharmacological properties support the notion that TAK-875, if effective in patients with type 2 diabetes, would have a low risk of provoking hypoglycemia. Recently, results were published from an exploratory randomized, double-blind study in 65 Japanese patients with type 2 diabetes who were treated with placebo or 100 or 400 mg TAK-875 once daily for 2 weeks (8). TAK-875 produced marked dose-dependent glucose-lowering effects and improvements in other indices of glycemic control. TAK-875 was well tolerated, and importantly, no hypoglycemia occurred.

Based on the above, the current placebo-controlled study was designed to evaluate the glycemic effects of a range of dosages of TAK-875 (6.25–200 mg) administered once daily for 12 weeks in Japanese patients with type 2 diabetes inadequately controlled by diet/exercise. Glimepiride (1 mg) once daily was administered in an open-label fashion to one of the randomized groups as an active control.

RESEARCH DESIGN AND METHODS

—This was a phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week dose-ranging evaluation of the novel GPR40 agonist TAK-875. A nonblinded group received glimepiride as an active control. The study was performed in 28 centers across Japan in accordance with the ethics principles set out in the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guideline for Good Clinical Practice. It was approved by the institu-

From the [1]Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, Kawasaki Medical School, Okayama, Japan; and the [2]Pharmaceutical Development Division, Takeda Pharmaceutical Company Limited, Osaka, Japan.
Corresponding author: Kohei Kaku, kka@med.kawasaki-m.ac.jp.
Received 6 May 2012 and accepted 7 August 2012.
DOI: 10.2337/dc12-0872. Clinical trial reg. no. japiccti-090972, www.japic.or.jp.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0872/-/DC1.

See accompanying commentary, p. 185.

tional review boards at each study site, and all subjects provided written informed consent.

The study comprised an 8-week screening period, a 12-week treatment period, and a 1-week follow-up period. The enrolled patients with type 2 diabetes were required to be aged ≥20 years at the start of screening (week −8) and to have an A1C level between ≥7.4 and <10.5% at screening (week −8) and 4 weeks later (week −4), despite receiving specific dietary and exercise therapy, which was initiated at least 4 weeks before the screening period. The main exclusion criteria were as follows: patients administered any antidiabetes drug within 4 weeks of the screening period or during the screening period; patients requiring insulin; patients with hepatic or renal impairment, serious cardiovascular, pancreatic or hematological disorders, or any malignancy; patients with a drug (including alcohol) abuse/dependency problem or with a hypersensitivity to any ingredient being administered; and pregnant or lactating women and those of child-bearing age not practicing adequate contraception.

Each subject visited the clinic 4 and 8 weeks after screening and, provided they met the eligibility criteria, on week 0 they were randomly allocated to receive double-blind therapy with 6.25, 12.5, 25, 50, 100, or 200 mg TAK-875; placebo; or nonblinded therapy with 1 mg glimepiride. All treatments were administered once daily before breakfast.

During the screening period, the following were recorded: demographics/patient characteristics, medical history, physical examination, body weight, vital signs, 12-lead electrocardiogram, clinical laboratory tests, pregnancy test, A1C, compliance with diet/exercise, and treatment-emergent adverse events (TEAEs). At randomization; after 2, 4, 6, 8, 10, and 12 weeks' treatment; and after an additional 1 week's follow-up, measurements included the following: vital signs, clinical laboratory tests, physical examination, body weight, concomitant medications, compliance with diet/exercise, and TEAEs. Measures of glycemic control such as A1C, fasting plasma glucose (FPG), insulin, glucagon, proinsulin, and C-peptide; glycoalbumin; and 1,5-anhydroglucitol (1,5-AG) as well as serum lipids were performed on weeks 0, 2, 4, 8, and 12. Plasma glucose, insulin, C-peptide, glucagon, total glucagon-like peptide 1 (GLP-1), and active GLP-1 levels were determined during a meal tolerance test (500 kcal; comprising ~51% carbohydrates, 38% fat, and 10% protein) at baseline and week 12. All week-12 assessments were performed at the end of treatment visit or upon discontinuation for patients who prematurely withdrew from the study.

Outcome measures

The primary end point was the change in A1C at week 12 from baseline. Secondary end points included changes in A1C, FPG, glycoalbumin, and 1,5-AG at each visit and the glucose, insulin, glucagon, C-peptide, and active GLP-1 responses to a meal tolerance test. Additional end points comprised other parameters of glycemic control such as insulinogenic index and serum lipids. Laboratory assessments were all performed at an independent central laboratory (Mitsubishi Chemical Medience, Tokyo, Japan). Values for A1C (%) were estimated using the National Glycohemoglobin Standardization Program equivalent values (%), which were calculated from the formula A1C (%) = 1.02 × A1C (Japan Diabetes Society) (%) + 0.25%. This takes into consideration the relation between A1C (Japan Diabetes Society) (%) determined using the previous Japanese standard measurement methods and A1C (National Glycohemoglobin Standardization Program) (9).

Safety measures

Safety was assessed by recording TEAEs, vital signs, body weight, 12-lead electrocardiogram, and clinical laboratory test results. TEAE reporting included investigator assessments for severity and relationship to study drug.

Statistical methods

On the basis of the result of a previous clinical study (8), 48 subjects per group were required to provide 90% power of detecting differences between the placebo and ≥25-mg TAK-875 dose groups. Allowing for withdrawals, we set the number of randomized subjects at 55 per group (440 in total).

Efficacy assessments included all randomized patients who received at least one dose of study medication. For the primary end point, least square means and corresponding two-sided 95% CIs were calculated by treatment group, and the differences between TAK-875 and the placebo groups were analyzed using an ANCOVA model with treatment as factor and baseline A1C as covariate. Two-sided hypothesis testing was performed at a

Table 1—*Baseline demographic and clinical characteristics*

	Placebo	TAK-875 (mg)						1 mg Glimepiride
		6.25	12.5	25	50	100	200	
n subjects	48	48	53	52	51	52	43	49
Age (years)	58.8 ± 8.3	57.5 ± 9.7	59.1 ± 10.1	59.7 ± 10.6	59.0 ± 11.3	57.2 ± 9.3	56.9 ± 11.7	54.5 ± 9.8
Male	31 (64.6)	35 (72.9)	30 (56.6)	35 (67.3)	40 (78.4)	42 (80.8)	23 (53.5)	32 (65.3)
Female	17 (35.4)	13 (27.1)	23 (43.4)	17 (32.7)	11 (21.6)	10 (19.2)	20 (46.5)	17 (34.7)
BMI (kg/m^2)	24.42 ± 3.37	24.30 ± 3.17	24.57 ± 4.23	24.92 ± 3.61	24.39 ± 3.24	24.86 ± 3.46	26.36 ± 5.72	24.44 ± 3.92
Duration of diabetes (years)	6.41 ± 6.09	7.58 ± 6.49	6.58 ± 5.54	6.62 ± 6.17	6.61 ± 6.39	6.77 ± 4.89	7.33 ± 6.62	5.46 ± 5.07
A1C (%)	8.50 ± 0.92	8.28 ± 0.75	8.48 ± 0.86	8.38 ± 0.91	8.41 ± 0.89	8.48 ± 0.82	8.55 ± 0.96	8.55 ± 0.83
FPG (mg/dL)	180.0 ± 33.1	174.7 ± 27.9	179.4 ± 36.9	173.4 ± 35.1	179.8 ± 35.5	180.7 ± 37.6	177.6 ± 35.0	176.7 ± 35.0

Data are means ± SD or *n* (%).

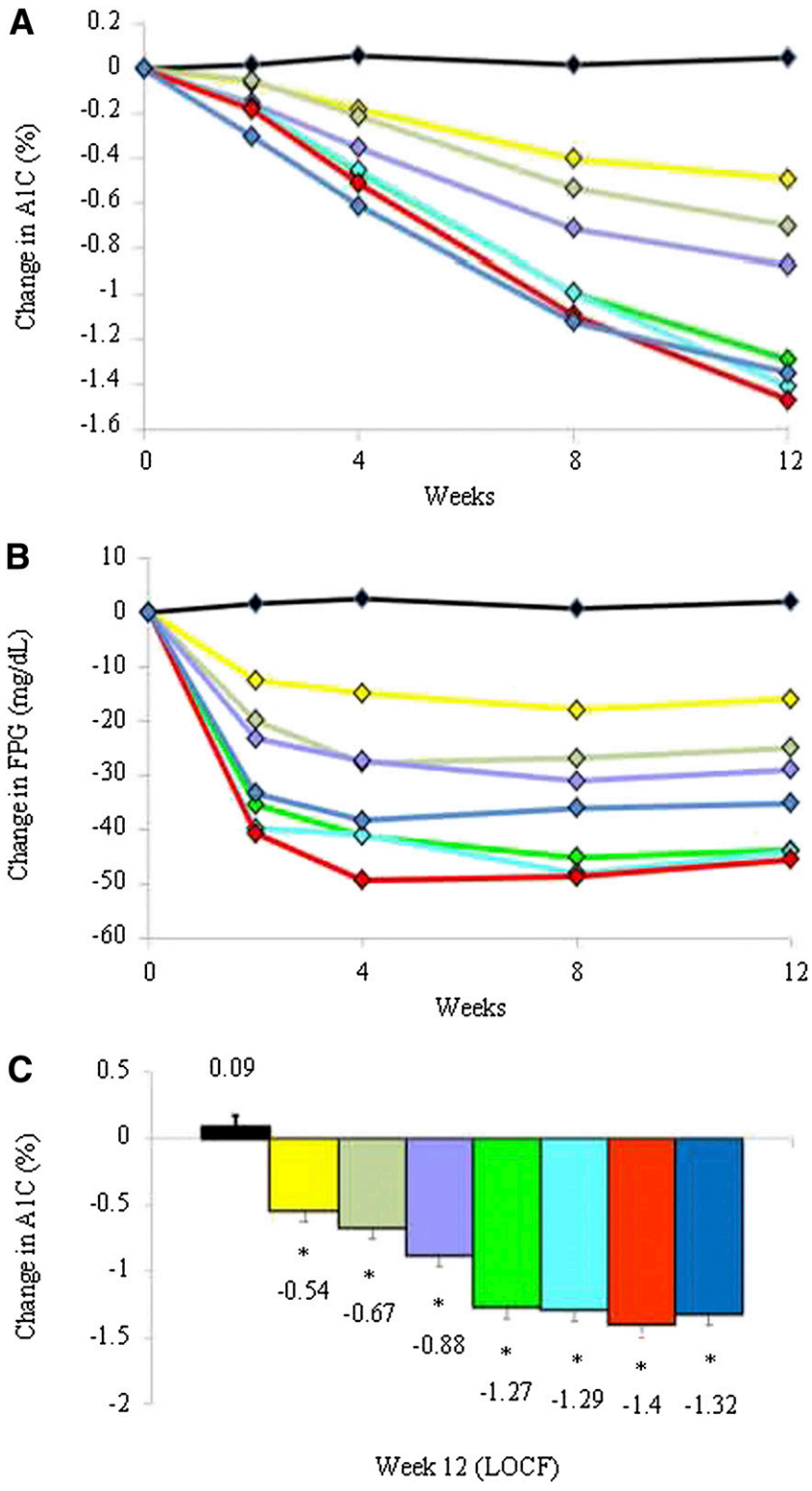

Figure 1—*Change in A1C (%)* (A)*, FPG (milligrams per deciliter)* (B)*, and primary end point (% change in A1C at week 12 [last observation carried forward {LOCF}] vs. baseline)* (C) *in a placebo-controlled study in patients with type 2 diabetes treated with 6.25–200 mg TAK-875 or 1 mg glimepiride. Placebo, black lines and column; 6.25 mg TAK-875, yellow lines and column; 12.5 mg TAK-875, light-green lines and column; 25 mg TAK-875, purple lines and column; 50 mg TAK-875, dark-green lines and column; 100 mg TAK-875, light-blue lines and column; 200 mg TAK-875, red lines and column; and 1 mg glimepiride, dark-blue lines and column.* *$P < 0.0001$ *vs. placebo (ANCOVA).*

significance level of 5%. Other efficacy end points were summarized for each visit by treatment group using descriptive statistics or frequency distributions.

Safety assessments included all patients who received at least one dose of study medication. Safety findings were summarized using descriptive statistics or frequency distributions.

RESULTS—Details of patient disposition are shown in Supplementary Fig. 1. Of 660 subjects who signed a consent form, 396 eligible patients were randomized to one of the eight treatment groups and 380 (96.0%) completed the study. In total, there were 268 men (67.7%) and 128 women (32.3%) with a mean age of 57.9 years and a mean duration of diabetes of 6.7 years. In the randomized population, the mean ± SD baseline A1C and FPG were 8.45 ± 0.86% and 177.8 ± 34.5 mg/dL, respectively. The eight groups were comparable for the majority of baseline characteristics (Table 1). Compliance with treatment and diet/exercise was high in all eight treatment groups with no significant differences between them.

Clinical efficacy

Figure 1*A–C* and Table 2 document the key findings associated with glycemic control after 12 weeks' treatment with 6.25–200 mg TAK-875, 1 mg glimepiride, and placebo. Mean reductions in A1C were rapid for all doses of TAK-875 and glimepiride. Significant decreases occurred as early as week 4 and continued to decline to week 12 ($P < 0.05$), when maximal effects were observed. The least square mean change in A1C at week 12 from baseline (primary end point) is shown in Fig. 1*C*. All TAK-875 groups had statistically significant decreases in A1C at week 12 compared with placebo ($P < 0.0001$).

1,5-AG was increased dose- and time-dependently in the TAK-875 groups, and after 12 weeks, the increases in all TAK-875 groups were significantly greater than those achieved with placebo (Table 2). Changes for other parameters such as fasting insulin, fasting C-peptide, fasting glucagon, and proinsulin were relatively modest in all groups (Table 2).

Results from meal tolerance tests confirm improved glycemic control with TAK-875 as evidenced by dose-dependent decreases in plasma glucose area under the curve $(AUC)_{0–2\ h}$ and 2-h plasma glucose levels. In addition, with the exception of the 6.25-mg dose of

Table 2—*Change in key glycemic efficacy end points after 12 weeks' treatment (last observation carried forward) versus baseline*

	Placebo	TAK-875 (mg)						1 mg Glimepiride
		6.25	12.5	25	50	100	200	
ΔA1C (%)	0.08 ± 0.65, *n* = 48	−0.49 ± 0.49, *n* = 48*	−0.68 ± 0.67, *n* = 53*	−0.86 ± 0.59, *n* = 52*	−1.25 ± 0.74, *n* = 51*	−1.30 ± 0.78, *n* = 52*	−1.43 ± 0.78, *n* = 42*	−1.35 ± 0.58, *n* = 49
ΔFPG (mg/dL)	3.2 ± 24.7, *n* = 48	−16.0 ± 25.5, *n* = 48*	−25.3 ± 33.1, *n* = 53*	−28.7 ± 21.5, *n* = 52*	−43.3 ± 28.2, *n* = 51*	−42.8 ± 28.0, *n* = 52*	−45.1 ± 31.3, *n* = 42*	−35.2 ± 29.0, *n* = 49*
Δ1,5-AG (μg/dL)	−0.15 ± 2.28, *n* = 48	1.40 ± 1.66, *n* = 48*	2.02 ± 3.21, *n* = 53*	3.65 ± 2.77, *n* = 52*	4.63 ± 3.22, *n* = 51*	5.19 ± 3.24, *n* = 52*	6.43 ± 4.53, *n* = 42*	4.19 ± 2.94, *n* = 49
ΔFasting insulin (μU/mL)	−0.54 ± 2.97, *n* = 47	−0.08 ± 3.04, *n* = 47	0.47 ± 4.95, *n* = 53	0.82 ± 3.15, *n* = 51*	0.71 ± 3.87, *n* = 51	0.17 ± 3.44, *n* = 52	0.99 ± 4.43, *n* = 42	1.33 ± 2.85, *n* = 49
ΔFasting C-peptide (ng/mL)	−0.12 ± 0.35, *n* = 48	−0.05 ± 0.44, *n* = 48	−0.04 ± 0.66, *n* = 53	0.11 ± 0.39, *n* = 52*	−0.06 ± 0.44, *n* = 51	0.09 ± 0.47, *n* = 52*	−0.04 ± 0.30, *n* = 42	0.02 ± 0.38, *n* = 49
ΔFasting glucagon (pg/mL)	1.6 ± 15.4, *n* = 48	4.3 ± 13.9, *n* = 48	1.4 ± 12.1, *n* = 53	5.9 ± 15.1, *n* = 52	4.4 ± 10.8, *n* = 51	4.1 ± 15.7, *n* = 52	7.9 ± 11.6, *n* = 42*	1.6 ± 14.0, *n* = 49
ΔProinsulin/insulin	0.033 ± 0.196, *n* = 47	−0.014 ± 0.173, *n* = 47	0.010 ± 0.156, *n* = 53	0.058 ± 0.307, *n* = 51	−0.041 ± 0.243, *n* = 51	−0.021 ± 0.240, *n* = 52	−0.075 ± 0.215, *n* = 42*	−0.058 ± 0.202, *n* = 49
Meal tolerance test								
Δ2-h PG (mg/dL)	6.2 ± 37.6, *n* = 46	−29.9 ± 37.7, *n* = 48*	−45.3 ± 53.8, *n* = 52*	−57.4 ± 44.3, *n* = 50*	−68.6 ± 40.4, *n* = 48*	−72.7 ± 37.8, *n* = 49*	−79.6 ± 49.3, *n* = 41*	−73.0 ± 51.5, *n* = 49
ΔPG $AUC_{0–2\ h}$ (mg · h/dL)	0.9 ± 60.4, *n* = 46	−56.8 ± 59.7, *n* = 48*	−84.8 ± 88.3, *n* = 52*	−91.9 ± 61.6, *n* = 50*	−122.2 ± 58.1, *n* = 48*	−129.2 ± 63.0, *n* = 49*	−139.3 ± 71.1, *n* = 41*	−107.5 ± 77.2, *n* = 49*
ΔInsulin $AUC_{0–2\ h}$ (μU · h/mL)	−5.94 ± 18.25, *n* = 46	−0.36 ± 10.98, *n* = 47	8.54 ± 17.74, *n* = 52*	7.22 ± 17.38, *n* = 48*	12.56 ± 18.31, *n* = 47*	10.90 ± 18.09, *n* = 49*	11.33 ± 21.58, *n* = 40*	25.22 ± 41.04, *n* = 48
ΔC-peptide $AUC_{0–2\ h}$ (ng · h/ml)	−0.61 ± 1.25, *n* = 46	−0.05 ± 1.09, *n* = 48*	0.38 ± 1.25, *n* = 52*	0.81 ± 1.46, *n* = 50*	0.87 ± 1.38, *n* = 48*	0.99 ± 1.32, *n* = 49*	0.81 ± 1.29, *n* = 41*	1.50 ± 1.81, *n* = 49
ΔGlucagon $AUC_{0–2\ h}$ (pg · h/mL)	−2.7 ± 29.3, *n* = 46	8.5 ± 24.8, *n* = 48*	1.7 ± 22.7, *n* = 52	6.4 ± 23.4, *n* = 50	5.0 ± 23.4, *n* = 48	3.5 ± 22.2, *n* = 49	−4.2 ± 23.2, *n* = 41	−3.5 ± 27.3, *n* = 49
ΔTotal GLP-1 $AUC_{0–2\ h}$ (pmol · h/L)	−0.019 ± 13.745, *n* = 46	5.806 ± 15.092, *n* = 48	2.076 ± 15.446, *n* = 52	5.045 ± 18.842, *n* = 50	3.961 ± 14.858, *n* = 48	3.747 ± 14.911, *n* = 49	9.143 ± 15.912, *n* = 41*	−3.267 ± 13.937, *n* = 49*
ΔActive GLP-1 $AUC_{0–2\ h}$ (pmol · h/L)	−1.521 ± 2.252, *n* = 46	−0.656 ± 2.880, *n* = 48	−1.090 ± 4.265, *n* = 51	−0.666 ± 2.930, *n* = 50	−0.232 ± 2.145, *n* = 48*	−0.399 ± 2.745, *n* = 48*	−0.072 ± 2.668, *n* = 41*	−1.780 ± 2.633, *n* = 49

Data are means ± SD unless otherwise indicated. PG, plasma glucose. *$P < 0.05$ vs. placebo. Parameters in glimepiride group were not compared with placebo.

TAK-875, both insulin and C-peptide were increased by TAK-875 and glimepiride during the meal tolerance test (Table 2). For example, insulin secretion, as estimated by the change from baseline in $AUC_{0–2\ h}$, was significantly increased by 12.5–200 mg TAK-875 (range 8.54–11.33 μU · h/mL, $P < 0.05$) but was increased to a greater extent by glimepiride (25.22 μU · h/mL, which was significantly greater versus 6.25, 12.5, 25, and 100 mg TAK-875 at week 12, $P < 0.05$). Other changes during the meal tolerance test were relatively modest. Total GLP-1 $AUC_{0–2\ h}$ showed an increasing tendency with all doses of TAK-875 (range 2.076–9.143 pmol · h/mL) compared with reductions in the case of placebo (−0.019 pmol · h/mL) and glimepiride (−3.267 pmol · h/mL).

Safety and tolerability

Safety and tolerability findings with TAK-875, glimepiride, and placebo, including TEAEs with an incidence of ≥5%, are summarized in Table 3. The overall incidence of TEAEs in each group was of the same frequency, and no dose-dependent changes in tolerability were observed in the TAK-875 groups. Nasopharyngitis was the most frequently reported TEAE in all groups. Five serious TEAEs were recorded: one case of lymphoma for 12.5 mg TAK-875, one case each of upper-respiratory tract inflammation and cholecystitis for 50 mg TAK-875, and one case each of colonic polyp and femoral neck fracture in 100 mg TAK-875. None of these serious TEAEs were considered drug related. No clinically relevant differences were found among the treatment groups for laboratory tests, vital signs, or 12-lead electrocardiogram. There were four mild episodes of hypoglycemia during the trial, none of which resulted in drug withdrawal: 2 of 49 (4.1%) cases in the glimepiride group, 2 of 299 (0.7%) cases in the combined TAK-875 groups, and one case each with 25 mg TAK-875 (1.9%) and 200 mg TAK-875 (2.3%). Increases in mean body weight after 12 weeks were greatest for 1 mg glimepiride (0.96 ± 1.70 kg) followed by 200 mg TAK-875 (0.76 ± 1.74 kg), 100 mg TAK-875 (0.62 ± 1.79 kg), and 50 mg TAK-875 (0.26 ± 1.94 kg) and were little changed (<0.1 kg increase) in all other treatment and placebo groups.

CONCLUSIONS—This study demonstrated that treatment with once-daily TAK-875 for 12 weeks produced clinically relevant and statistically significant reductions in A1C and FPG versus placebo in patients with type 2 diabetes inadequately controlled by diet/exercise. TAK-875 at 50–200-mg doses reduced A1C to an extent similar to the reduction achieved with 1 mg glimepiride once daily. Furthermore, TAK-875 significantly reduced the exposure of patients to high glucose levels during a meal tolerance test as demonstrated by dose-dependent decreases in plasma glucose $AUC_{0–2\ h}$ and 2-h plasma glucose levels. These results are consistent with a previous short-term exploratory study that was undertaken in Japanese patients with type 2 diabetes (8). They are also in close agreement with a similarly designed dose-ranging study performed in the U.S. and Central America (10). In this latter study, once-daily treatment with 50–200 mg TAK-875 for 12 weeks reduced A1C by 0.65% at a dosage of 6.25 mg to ~1.0% at doses of ≥50 mg. Comparable values in our study were −0.54% at 6.25 mg to approximately −1.27% at doses ≥50 mg.

Total GLP-1 secretion showed an increasing tendency with all doses of TAK-875 (range 2.076–9.143 pmol · h/mL) compared with a reduction in the case of glimepiride (−3.267 pmol · h/mL). Results from animal studies suggest that increased GLP-1 secretion through stimulation of GPR40 may play a role in regulating glucose and overall energy homeostasis (11). It has been suggested that a direct effect of TAK-875 on activation of intestinal GPR40 may increase GLP-1, which in turn augments insulin secretion (10). However, the clinical effects of TAK-875 on GLP-1 secretion require clarification in a more dedicated study in the future.

One of the main goals of this phase 2 dose-ranging study was to ascertain the benefit to risk properties of the various

Table 3—*Treatment-emergent adverse events reported during 12-week study, including those with an incidence of ≥5%*

		TAK-875 mg						1 mg
	Placebo	6.25	12.5	25	50	100	200	Glimepiride
Subjects	48	48	53	52	51	52	43	49
Patients with at least 1 AE (%)	31 (64.6)	24 (50.0)	27 (50.9)	28 (53.8)	25 (49.0)	28 (53.8)	23 (53.5)	30 (61.2)
Events	53	34	50	40	45	61	40	56
Serious AEs (%)	0	0	1 (1.9)	0	2 (3.9)	2 (3.8)	0	0
Serious AEs related to treatment	0	0	0	0	0	0	0	0
Subjects with an AE who discontinued treatment	0	0	2 (3.8)	3 (5.8)	2 (3.9)	1(1.9)	0	0
TEAEs reported in ≥5% of subjects by preferred term								
Nasopharyngitis	8 (16.7)	5 (10.4)	11 (20.8)	5 (9.6)	6 (11.8)	5 (9.6)	7 (16.3)	3 (6.1)
Upper-respiratory tract inflammation	2 (4.2)	4 (8.3)	1 (1.9)	0	3 (5.9)	2 (3.8)	0	1 (2.0)
Contusion	3 (6.3)	1 (2.1)	3 (5.7)	0	0	2 (3.8)	0	0
Back pain	0	0	0	0	2 (3.9)	2 (3.8)	1 (2.3)	3 (6.1)
Constipation	0	0	3 (5.7)	1 (1.9)	1 (2.0)	0	1 (2.3)	1 (2.0)
Blood uric acid increased	1 (2.1)	0	0	1 (1.9)	3 (5.9)	0	0	1 (2.0)
Headache	0	0	1 (1.9)	1 (1.9)	1 (2.0)	3 (5.8)	0	0

Data are *n* or *n* (%). AE, adverse event.

dosages of TAK-875 administered to patients with type 2 diabetes. At the completion of the treatment (week 12), A1C was decreased both statistically and clinically significantly in all the TAK-875 dose groups compared with placebo. Furthermore, treatment with TAK-875 was well tolerated over the 12-week treatment period, with the majority of adverse events being mild in intensity. Importantly, there were no dose-related trends relating to tolerability and safety, and no serious TEAEs were considered to be treatment related by the investigators. None of the safety findings reported during the current study would influence the decision regarding optimal starting dosage with TAK-875.

A key concern with new therapies for reducing the hyperglycemic risk associated with type 2 diabetes is the potential to excessively reduce glucose levels and cause episodes of hypoglycemia. The novel mode of action of TAK-875 via GPR40-stimulated glucose-dependent increase in insulin secretion (6) has been proposed as a mechanism that would pose low risk of causing hypoglycemia (2,7). In this study, mild hypoglycemia occurred less frequently in the TAK-875 groups (0.7%) than in the glimepiride group (4.1%). The incidence of hypoglycemia in the TAK-875 groups was not dose dependent. These data are consistent with the U.S./Central American study that reported an incidence rate of mild hypoglycemia, which was similar for 6.25–200 mg TAK-875 and placebo, and this rate was significantly lower than that reported for glimepiride (10). On the basis of these findings and the efficacy results discussed above, TAK-875 is equally effective and well tolerated in Japanese and in North and Central American patients with type 2 diabetes.

This phase II study included a 12-week treatment period, which is a short duration for a disease that will likely need to be treated lifelong. After 12 weeks, the decrease in mean A1C had reached a maximum level and may have further decreased if the duration of treatment had been extended. A further limitation is that glimepiride therapy was administered in an open-label manner, which may introduce some bias with regard to the active comparator.

In conclusion, TAK-875 produced clinically and statistically significant improvements in A1C, FPG, and responses to a meal tolerance test in patients with type 2 diabetes inadequately controlled by diet/exercise. The effect of doses of 50–200 mg once daily was comparable with that of 1 mg glimepiride once daily. All doses of TAK-875 were well tolerated, and the majority of TEAEs were mild and rarely resulted in discontinuation of therapy.

Acknowledgments—This study was funded by Takeda Pharmaceutical Company Limited. K.K. has received research funding, consultancy fees, or lecture fees from Astellas, AstraZeneca, Merck Sharpe & Dohme, Daiichi-Sankyo, Dainippon-Sumitomo, Novartis, Novo Nordisk, sanofi-aventis, Sanwa, and Takeda Pharmaceutical Company Limited. T.A. and R.Y. are employees of Takeda Pharmaceutical Company Limited, Osaka, Japan. No other potential conflicts of interest relevant to this article were reported.

Takeda Pharmaceutical Company Limited was responsible for study design, data collection and management, and statistical analyses. The trial was independently monitored. The investigators were responsible for the interpretation of the data and the preparation of the submitted publication, having full access to all clinical findings.

K.K. was the chief independent medical expert for this study and was involved in the design of the clinical trial and interpretation of the findings, and reviewed and approved the final version of the manuscript. T.A. was involved in the design of the clinical trial and interpretation of the findings; was responsible for drafting the report and critical revision of important intellectual content, having full access to study data; and approved the final version of the manuscript. R.Y. was involved in the design of the clinical trial, day-to-day management, and data collection and interpretation and reviewed and approved various versions of the manuscript, including the final version. K.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank all investigators (listed in Supplementary Data online) for their assistance with this study. The authors thank the sponsor for assistance with data monitoring and gathering and for funding editorial writing that was provided by Steve Clissold, Content Ed Net.

References

1. Haber EP, Ximenes HM, Procópio J, Carvalho CR, Curi R, Carpinelli AR. Pleiotropic effects of fatty acids on pancreatic β-cells. J Cell Physiol 2003;194:1–12
2. Stoddart LA, Smith NJ, Milligan G. International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, -2, and -3: pharmacology and pathophysiological functions.Pharmacol Rev 2008;60:405–417
3. Itoh Y, Kawamata Y, Harada M, et al. Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40. Nature 2003;422:173–176
4. Nagasumi K, Esaki R, Iwachidow K, et al. Overexpression of GPR40 in pancreatic β-cells augments glucose-stimulated insulin secretion and improves glucose tolerance in normal and diabetic mice. Diabetes 2009;58:1067–1076
5. Kebede M, Alquier T, Latour MG, Semache M, Tremblay C, Poitout V. The fatty acid receptor GPR40 plays a role in insulin secretion in vivo after high-fat feeding. Diabetes 2008;57:2432–2437
6. Negoro N, Sasaki S, Mikami S, et al. Discovery of TAK-875: a potent, selective, and orally bioavailable GPR40 agonist. ACS Med Chem Lett 2010;1:290–294
7. Naik H, Vakilynejad M, Wu J, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamic properties of the GPR40 agonist TAK-875: results from a double-blind, placebo-controlled single oral dose rising study in healthy volunteers. J Clin Pharmacol 2012;52:1007–1016
8. Araki T, Hirayama M, Hiroi S, Kaku K. GPR40-induced insulin secretion by the novel agonist TAK-875: first clinical findings in patients with type 2 diabetes. Diabetes Obes Metab 2012;14:271–278
9. Kashiwagi A, Kasuga M, Araki E, et al.; Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diab Invest 2012;3:39–40
10. Burant CF, Viswanathan P, Marcinak J, et al. TAK-875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2012;379:1403–1411
11. Edfalk S, Steneberg P, Edlund H. Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. Diabetes 2008;57:2280–2287