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ORIGINAL ARTICLE

Efficacy and safety of fasiglifam (TAK-875), a G protein-coupled receptor 40 agonist, in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial

K. Kaku[1], K. Enya[2], R. Nakaya[2], T. Ohira[2] & R. Matsuno[2]

[1] *Department of Medicine, Kawasaki Medical School, Okayama, Japan*
[2] *Pharmaceutical Development Division, Takeda Pharmaceutical Company Limited, Osaka, Japan*

Aim: To assess the efficacy and safety of fasiglifam 25 and 50 mg in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise.
Methods: This phase III, double-blind, placebo-controlled, multicentre study included 192 patients randomized to once-daily treatment with fasiglifam 25 mg (n = 63) or 50 mg (n = 62) or placebo (n = 67) for 24 weeks. The primary efficacy endpoint was the change from baseline in glycated haemoglobin (HbA1c) at week 24.
Results: At week 24, both fasiglifam groups had significantly reduced HbA1c levels compared with the placebo group ($p < 0.0001$). The least squares mean change from baseline in HbA1c was 0.16% with placebo, −0.57% with fasiglifam 25 mg and −0.83% with fasiglifam 50 mg. The percentage of patients who achieved an HbA1c target of <6.9% at week 24 was also significantly higher ($p < 0.05$) for fasiglifam 25 mg (30.2%) and 50 mg (54.8%) compared with placebo (13.8%). Fasiglifam significantly reduced fasting plasma glucose levels at all assessment points, starting from week 2. The incidence and types of treatment-emergent adverse events in each fasiglifam group were similar to those in the placebo group, and hypoglycaemia was reported in 1 patient receiving fasiglifam 50 mg. There were no clinically meaningful changes in body weight in any treatment group.
Conclusions: Fasiglifam significantly improved glycaemic control and was well tolerated, with a low risk of hypoglycaemia in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise; however, in a recent review of data from overall fasiglifam global clinical trials, concerns about liver safety arose and the clinical development of fasiglifam was terminated after this trial was completed.
Keywords: fasiglifam, GPR40, Japanese patients, TAK-875, type 2 diabetes

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Introduction

Type 2 diabetes is fast becoming a worldwide epidemic which is placing an enormous burden on global healthcare systems and resources [1,2]. Persistent uncontrolled hyperglycaemia is the hallmark metabolic abnormality of type 2 diabetes and is attributable largely to ongoing deterioration of insulin-secreting pancreatic β-cell function, which is characterized by both insulin resistance and/or secretory failure [3,4]. There is now abundant scientific evidence supporting the notion that achievement of tight glycaemic control will substantially reduce hyperglycaemia-related morbidity [5–8]. This would be relatively straightforward if sufficient insulin could be administered to reduce glucose levels to within the 'normal' range, but this ignores the devastating effects of hypoglycaemia, the most feared adverse consequence of glucose-lowering therapy [9–11]. A wide range of antidiabetic agents have been developed to help improve glycaemic control in patients with type 2 diabetes mellitus and, in Japan, insulin secretagogues, such as sulphonylureas, are commonly used, either as monotherapy or in combination regimens [12–14]. Sulphonylureas stimulate insulin secretion by selectively targeting ATP-regulated K^+ channels in the plasma membrane of pancreatic β cells. This mechanism is independent of plasma glucose levels, however, and thus increases the risk of hypoglycaemia [15,16]. This has led to a search for agents that can augment insulin secretion depending on the circulating glucose level, so as to minimize the chances of hypoglycaemia. In this regard, recent interest has centred on long-chain fatty acids which have been shown to amplify glucose-stimulated insulin secretion from pancreatic β-cells; this effect is mediated through activation of the G protein-coupled receptor 40 (GPR40), also known as free fatty acid receptor 1 [17,18]. It has been suggested that selective GPR40 agonists may potentiate nutrient-induced insulin secretion and this will favour enhanced prandial secretion and reduce the risk of interprandial hypoglycaemia [19].

Fasiglifam, an orally bioavailable GPR40 agonist, has been shown to produce marked dose-dependent glucose-lowering effects and improvements in other indices of glycaemic control [20–22]. In exploratory and dose-finding studies published to

Correspondence to: Kohei Kaku, 577, Matsushima, Kurashiki-shi, Okayama 701-0192, Japan.
E-mail: kka@med.kawasaki-m.ac.jp

date in the USA/Central America and Japan, it has been well tolerated and did not increase the risk of hypoglycaemia [23–25]. Indeed, in the US study it was associated with a significantly lower rate of hypoglycaemia than was glimepiride [25].

Based on the antihyperglycaemic effects and overall tolerability of fasiglifam reported in the pilot and dose-ranging studies, it was decided in the present phase III placebo-controlled trial to evaluate the glycaemic effects and safety of fasiglifam 25 and 50 mg administered once daily for the longer duration of 24 weeks in Japanese patients with type 2 diabetes inadequately controlled by diet/exercise. Concerns relating to liver safety, however, after a review of data obtained during the clinical trials' programme, resulted in termination of the development of fasiglifam after the present trial was completed.

Methods

This was a phase III, multicentre (21 clinical institutions in Japan), randomized, double-blind, parallel group, placebo-controlled 24-week comparative study in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. After a 4-week screening period, a 24-week treatment period in which patients were randomly assigned to receive either placebo or fasiglifam (25 or 50 mg) followed by a 1-week follow-up period was initiated. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Harmonized Tripartite Guideline for Good Clinical Practice. All participants provided written informed consent. Central or local institutional review boards approved the protocol at each study site.

Patients eligible for the study were aged ≥20 years and had type 2 diabetes mellitus with a glycated haemoglobin (HbA1c) level of between 6.9 and 10.4% at the start of the screening period. All patients had received specific dietary and exercise therapy for at least 8 weeks before the start of screening. Patients were excluded if they had been treated with any antidiabetic drug within 8 weeks before the start of screening or during the screening period, or if they had systolic blood pressure of ≥180 mmHg or diastolic blood pressure of ≥110 mmHg. Additionally, patients with requirement for insulin, those with hepatic or renal impairment, and those with serious cardiovascular, pancreatic or haematological disorders, or with any malignancy were also excluded. Pregnant or lactating women and those of child-bearing age who were not using contraception were not eligible.

Each participant visited the institution at the start and completion of the screening period (weeks −4 and 0) and on weeks 2, 4, 8, 12, 16, 20, 24 and 25. Provided they met the eligibility criteria during week 0, they were randomly allocated to receive double-blind therapy with fasiglifam 25 or 50 mg, or placebo. All treatments were administered as identical tablets once daily before breakfast.

During the 4-week screening period, the following were recorded: demographics/patient characteristics, medical history, concomitant medications, physical examination details, body weight, vital signs, 12-lead ECG (repeated on weeks 12 and 24), clinical laboratory test results, pregnancy test (repeated on week 24), measures of glycaemic control [HbA1c, fasting plasma glucose (FPG), fasting insulin, fasting C-peptide, fasting glucagon and fasting proinsulin levels], adiponectin, compliance with diet/exercise, and pretreatment-emergent adverse events. On weeks 2, 4, 8, 12, 16, 20 and 24 and after an additional 1 week's follow-up, the following measurements were performed: physical examination, body weight, vital signs, concomitant medications, clinical laboratory tests, compliance with diet/exercise, measures of glycaemic control, such as HbA1c, FPG, fasting insulin, fasting C-peptide, fasting glucagon and fasting proinsulin levels (but not at the follow-up visit), and treatment-emergent adverse events (TEAEs). All assessments were performed at the end of the treatment period at week 24 or at the point of discontinuation for patients who prematurely withdrew from the study.

The study was registered under clinical trials number: JapicCTI-111604.

Efficacy and Safety Outcome Measures

The primary endpoint was the change from baseline in HbA1c at week 24 [last observation carried forward (LOCF)]. Secondary endpoints included changes in HbA1c, FPG, fasting insulin, fasting C-peptide and fasting glucagon levels. Safety was assessed by recording all TEAEs using the Medical Dictionary for Regulatory Activities terminology, vital signs, 12-lead ECG, clinical laboratory test results and body weight. TEAE reporting included investigator assessments for severity, time of onset and relationship to study drug.

All clinical laboratory tests were performed at an independent central laboratory (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Values for HbA1c (%) were estimated using the National Glycohaemoglobin Standardization Program (NGSP) equivalent values (%), which were calculated using the formula: HbA1c (NGSP) (%) = 1.02 × HbA1c (Japan Diabetes Society) (%) + 0.25%. This equation takes into consideration the relationship between HbA1c (Japan Diabetes Society) (%) calculated using the previous Japanese standard measurement methods and HbA1c (NGSP) [26].

Exploratory endpoints included fasting proinsulin, homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of β-cell function (HOMA-β), proinsulin/insulin ratio, adiponectin and high-molecular-weight adiponectin. HOMA-IR and HOMA-β were calculated using the following formulas: HOMA-IR = fasting insulin (μIU/ml) × fasting glucose (mg/dl)/405, HOMA-IR = 360 × [fasting insulin (μIU/ml)/(fasting glucose (mg/dl) − 63)], respectively.

Statistical Methods

Sample size was calculated based on the results of two dose-ranging studies performed in the USA/Central America and Japan [24,25]. A total of 60 participants per group (180 participants in all) was assumed to have >90% of power using two sample t-tests to detect differences in the primary endpoint between both fasiglifam groups and placebo [−1.10% in 50 mg and −0.70% in 25 mg vs placebo with a common standard deviation (s.d.) per group of 1.10%] at a significance level of 5%.

The full analysis set was used to evaluate efficacy and included all patients randomly assigned to treatment groups

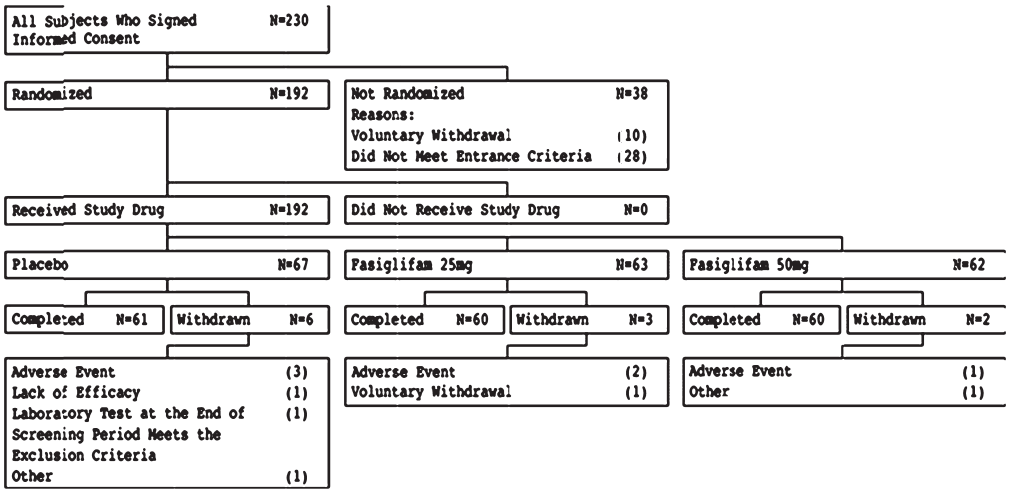

Figure 1. Participant disposition.

who received at least one dose of double-blind study drug. Missing values of week 24 were imputed by LOCF using any post-baseline values. No evaluable data were excluded for any reason. For the primary endpoint, an analysis of covariance model with study treatment as a fixed effect and baseline HbA1c as a covariate was performed. Based on this model, least squares (LS) means, standard error (s.e.) values, and corresponding two-sided 95% confidence intervals (CIs) were calculated for each treatment group. Both fasiglifam groups were compared with placebo based on a stepwise testing procedure. Two-sided hypothesis testing was performed at a significance level of 5%. Other efficacy endpoints were summarized at each visit by treatment group using descriptive statistics or frequencies, and exploratory two-sided 95% CIs for differences between treatment groups were also calculated.

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 Figure 1. Of 230 patients who signed a consent form, 192 eligible patients were randomized to placebo (n = 67), fasiglifam 25 mg (n = 63) or fasiglifam 50 mg (n = 62), and 181 (94.3%) completed the study. In total, there were 136 men (70.8%) and 56 women (29.2%) with a mean age of 60.4 years, a mean body mass index of 24.97 kg/m^2, and a mean duration of diabetes of 5.6 years. In the randomized population the mean (s.d.) baseline HbA1c and FPG were 7.79 (0.835)% and 8.63 (1.73) mmol/l, respectively. Baseline characteristics were generally similar among all treatment groups (Table 1). Compliance with treatment, diet and exercise was high and very similar in all treatment groups.

Clinical Efficacy

At week 24, both fasiglifam groups had a significant reduction in HbA1c compared with the placebo group ($p < 0.0001$; Figure 2A). The LS mean change from baseline in HbA1c was 0.16% with placebo, −0.57% with fasiglifam 25 mg and −0.83% with fasiglifam 50 mg. The placebo-corrected LS mean (95% CI) reduction from baseline in HbA1c was −0.75% (−0.985, −0.521) with fasiglifam 25 mg and −1.01% (−1.244, −0.777) with fasiglifam 50 mg. The mean change from baseline in HbA1c showed a time-dependent decrease from weeks 2 to 24

Table 1. Baseline demographic and clinical characteristics.

		Fasiglifam		
Placebo		**25 mg**	**50 mg**	**Total**
No. of participants	67	63	62	192
Age (years)	61.1 (9.2)	60.2 (10.5)	59.8 (10.9)	60.4 (10.1)
Male	46 (68.7)	43 (68.3)	47 (75.8)	136 (70.8)
Female	21 (31.3)	20 (31.7)	15 (24.2)	56 (29.2)
BMI (kg/m^2)	24.85 (3.70)	24.79 (3.90)	25.27 (3.60)	24.97 (3.72)
Duration of diabetes (years)	6.66 (6.50)	5.01 (4.41)	5.00 (4.43)	5.58 (5.27)
HbA1c (%)	7.83 (0.917)	7.84 (0.847)	7.69 (0.728)	7.79 (0.835)
FPG (mmol/l)	8.69 (1.69)	8.66 (1.73)	8.54 (1.78)	8.63 (1.73)
Fasting insulin (μIU/ml)	6.96 (3.837)	7.28 (7.807)	7.21 (4.669)	7.15 (5.644)

Data are mean (s.d.) or number of participants (%). BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin.

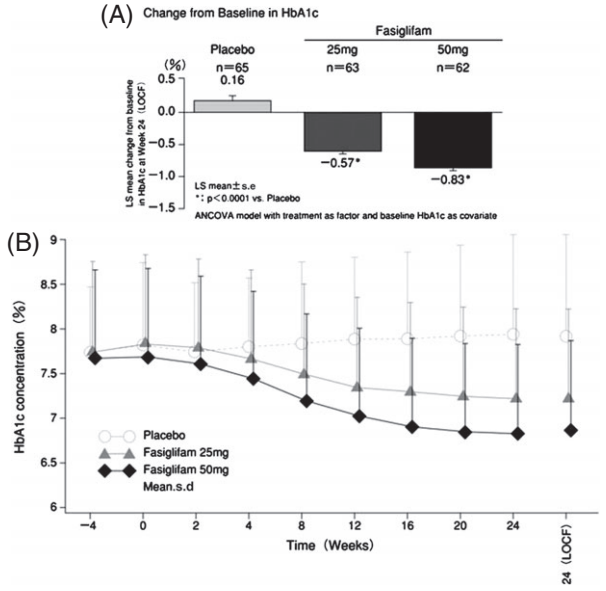

Figure 2. Change in glycated haemoglobin (HbA1c; %). (A) Primary endpoint least squares (LS) mean change from baseline at week 24 (LOCF). Error bars show standard error (s.e.) values. *p < 0.0001 versus placebo [analysis of covariance (ANCOVA)]. (B) Mean ± standard deviation (s.d.) values over time.

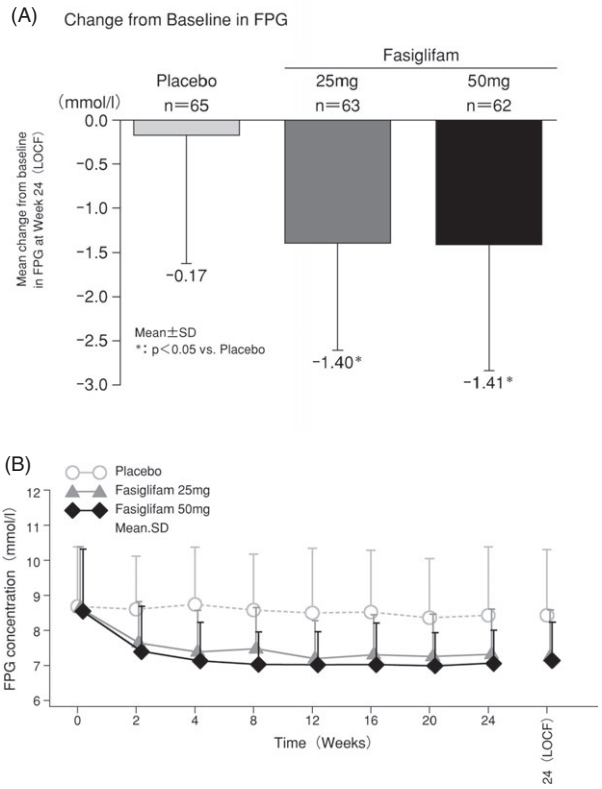

Figure 3. Change in fasting plasma glucose (FPG, mmol/l). (A) Mean ± standard deviation (s.d.) change from baseline at week 24 (last observation carried forward). *p < 0.05 versus placebo. (B) Mean ± s.d. values overtime.

in both fasiglifam groups and significant decreases occurred as early as week 4 compared with placebo (Figure 2B). The percentage of patients who achieved the clinical response target [HbA1c level <6.9% (based on the Japanese guideline)] [27] at week 24 was significantly higher in both fasiglifam groups than in the placebo group: 13.8% (9/65 participants) in the placebo group, 30.2% (19/63 participants) in the fasiglifam 25 mg group, 54.8% (34/62 participants) in the fasiglifam 50 mg group (2/67 participants in the placebo group had no post-baseline values of HbA1c and were excluded from the clinical response analysis). Differences (95% CI) in the percentages between the fasiglifam groups and placebo were 16.3% (2.208, 30.417) with fasiglifam 25 mg and 41.0% (26.028, 55.957) with fasiglifam 50 mg. Significant reductions from baseline were recorded for FPG in both fasiglifam groups compared with placebo at week 24 (Figure 3A). The mean change from baseline in FPG was −0.17 mmol/l with placebo, −1.40 mmol/l with fasiglifam 25 mg and −1.41 mmol/l with fasiglifam 50 mg. Differences (95% CI) in the mean changes from baseline in FPG between the fasiglifam groups and placebo were −1.23 mmol/l (−1.70, −0.76) for fasiglifam 25 mg and −1.24 mmol/l (−1.75, −0.73) for fasiglifam 50 mg. The reduction from baseline in FPG occurred from week 2 onwards in both fasiglifam groups, and the reduction was greater in these two groups compared with placebo at all assessment points during treatment (Figure 3B).

With regard to other glycaemic measures, such as change in fasting insulin, fasting C-peptide, fasting glucagon, fasting proinsulin, HOMA-IR, proinsulin/insulin ratio, adiponectin or high-molecular-weight adiponectin, no significant differences were recorded at week 24 in the fasiglifam groups compared with the placebo group. In contrast, HOMA-β was significantly increased by both dosages of fasiglifam compared with placebo at all assessment points except for week 24 (Figure S1).

Subgroup analyses were performed on the primary endpoint for baseline patient's characteristics. HbA1c was decreased at week 24 in the fasiglifam groups compared with the placebo group in all subgroups. The reductions in HbA1c in the fasiglifam groups tended not to be affected by age, gender, BMI or duration of diabetes (data not shown), but were larger when baseline HbA1c levels were higher. Thus, in patients with a baseline HbA1c ≥8.4%, decreases were 1.37 and 1.40% in the fasiglifam 25 and 50 mg groups, respectively, compared with decreases of 0.41 and 0.62% in those with a baseline HbA1c <8.4%.

Safety and Tolerability

Safety and tolerability findings with fasiglifam 25 and 50 mg and placebo, including TEAEs with an incidence of 5% or higher, are summarized in Table 2. The overall incidence of TEAEs was similar for the fasiglifam and placebo groups. All events with fasiglifam were mild or moderate in severity, and there was a slightly higher incidence of treatment-related TEAEs in the fasiglifam 50 mg group (14.5% vs ~6% in the other two groups). The incidence of TEAEs leading to treatment discontinuation was similar between treatments. Serious TEAEs were reported in 1 patient on placebo (renal cell carcinoma) and 2 patients on 25 mg fasiglifam (one each of abnormal hepatic

Table 2. Summary of treatment-emergent adverse events.

		Fasiglifam, n (%)	
	Placebo, n (%)	25 mg	50 mg
Number of participants	67	63	62
Patients with any TEAEs	40 (59.7)	37 (58.7)	35 (56.5)
Patients with any TEAEs: mild	35 (52.2)	31 (49.2)	35 (56.5)
Patients with any TEAEs: moderate	5 (7.5)	6 (9.5)	0
Patients with any TEAEs: severe	0	0	0
Patients with any treatment-related TEAEs	4 (6.0)	4 (6.3)	9 (14.5)
Patients with any TEAEs leading to drug discontinuation	3 (4.5)	2 (3.2)	1 (1.6)
Patients with any treatment-emergent serious AEs	1 (1.5)	2 (3.2)	0
Deaths	0	0	0
Patients with any TEAEs and a frequency of at least 5% in any group			
Nasopharyngitis	11 (16.4)	11 (17.5)	9 (14.5)
Upper respiratory tract inflammation	1 (1.5)	5 (7.9)	5 (8.1)
Patients with any treatment-related TEAEs			
Lymphadenopathy	1 (1.5)	0	0
Constipation	1 (1.5)	0	0
Feeling abnormal	0	0	1 (1.6)
Hepatic function abnormal	0	1 (1.6)	1 (1.6)
Cholelithiasis	0	0	1 (1.6)
Bronchitis	0	0	1 (1.6)
Increased alanine aminotransferase	0	1 (1.6)	3 (4.8)
Increased aspartate aminotransferase	0	1 (1.6)	0
Blood creatine phosphokinase increased	0	1 (1.6)	0

TEAEs are listed in order of severity. Each participant was counted only once by maximum severity of Preferred Term or System Organ Class. AE, adverse event; TEAE, treatment-emergent AE.

function and uterine cancer). The case of abnormal hepatic function was moderate in severity and led to discontinuation of fasiglifam 25 mg with full recovery. The most commonly reported TEAEs in the fasiglifam groups were nasopharyngitis and upper respiratory tract inflammation. Hypoglycaemia was reported in 1 participant receiving fasiglifam 50 mg, which was mild in severity and did not lead to discontinuation of study treatment.

The incidence of alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN) was slightly higher in the fasiglifam 50 mg (6.5%, n = 4) and 25 mg (4.8%, n = 3) groups than in the placebo group (1.5%, n = 1). The incidence of ALT ≥5 times the ULN was similar among all treatment groups: fasiglifam 50 mg, 0% (n = 0); fasiglifam 25 mg, 1.6% (n = 1); and placebo, 1.5% (n = 1). The ALT abnormalities were observed at different time periods in the fasiglifam groups: at week 4 in 1 participant, weeks 8–12 in 3 participants, and weeks 16–24 in 3 participants. Follow-up of the 7 fasiglifam-treated participants with ALT >3× ULN revealed that in 5 participants, levels returned to normal or back to baseline within 4 weeks, either during continued treatment (3 participants) or after stopping study treatment (2 participants). In 2 participants, ALT increases occurred at week 24 and, in both these participants, ALT levels also decreased during the extended follow-up period. Five of 7 fasiglifam-treated participants had evidence of hepatic steatosis. The incidence of other abnormal liver tests [aspartate aminotransferase (AST), alkaline phosphatase or γ-glutamyltransferase ≥3× ULN or total bilirubin ≥2× ULN] were similar among all treatment groups. Study treatment was discontinued in only 1 participant each in the placebo, fasiglifam 25 mg and fasiglifam 50 mg groups, respectively. The participant in the fasiglifam 25 mg group experienced a serious TEAE of abnormal hepatic function (ALT 10× ULN and total bilirubin 3× ULN) which was accompanied by epigastric pain, and gallstones, biliary sludge and adenomyomatosis (confirmed by medical imaging). The participant in the fasiglifam 50 mg group had a TEAE of increased ALT (approximately 4× ULN), and the participant in the placebo group had TEAEs of increased ALT and AST levels, approximately 6× ULN and 3× ULN, respectively. No other participants discontinued study treatment as a result of a hepatic adverse event.

No clinically meaningful differences were found among the treatment groups for vital signs or 12-lead ECGs. There were no clinically meaningful changes in body weight in any treatment group: the mean (s.d.) change from baseline was −0.88 kg (2.84) with placebo, 0.42 kg (1.66) with fasiglifam 25 mg and 0.44 kg (2.09) with fasiglifam 50 mg.

Discussion

One of the main goals of the present phase III comfirmatory study was to ascertain the benefit-to-risk properties of the GPR40 agonist fasiglifam in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. Fasiglifam 25 and 50 mg administered orally once daily for 24 weeks produced clinically relevant and significant reductions in HbA1c and FPG versus placebo. The percentage of participants who achieved an HbA1c level of <6.9% was 30.2% in the fasiglifam 25 mg group, 54.8% in the fasiglifam 50 mg group and 13.8% in the placebo group, showing that more

than half of participants achieved the glycaemic control target with the fasiglifam monotherapy. These results are consistent with previous 12-week dose-ranging studies performed in the USA/Central America and Japan in patients with type 2 diabetes [24,25]. In a Japanese dose-ranging study [24], LS mean change from baseline in HbA1c at week 12 was 0.09% with placebo, −0.88% with fasiglifam 25 mg and −1.27% with fasiglifam .50 mg. While the reductions in HbA1c were slightly less in the present study, HbA1c levels at baseline were lower. Since the subgroup analysis showed that HbA1c tended to be reduced more in participants with higher HbA1c levels at baseline, the smaller reduction in HbA1c in the present study might be associated with the lower HbA1c baseline level.

Overall, the incidence of TEAEs in each group was similar for the fasiglifam and placebo groups with the majority of TEAEs being mild in severity. There was a slightly higher incidence of TEAEs in the fasiglifam 50 mg group, but this was not considered clinically relevant and there was no difference between fasiglifam and placebo regarding the number of participants discontinuing treatment as a result of a TEAE. As noted earlier, hypoglycaemia is the most feared TEAE associated with type 2 diabetes and agents that can reduce glucose levels without causing episodes of hypoglycaemia would be advantageous. The novel mode of action of fasiglifam, via GPR40-stimulated glucose-dependent increases in insulin secretion [17], has been proposed as a mechanism which would pose a low risk of causing hypoglycaemia [14,18]. The US/Central American study reported an incidence rate of mild hypoglycaemia for fasiglifam 6.25–200 mg (2%) that was similar to that for placebo (3%), and these rates were significantly lower than the rate of 19% reported for glimepiride [22]. Similarly, in a Japanese dose-ranging study the incidence of mild hypoglycaemia was 0.7% with fasiglifam compared with 4.1% for glimepiride, and no dose-dependent trends were observed [21]. In the present study, which was twice the duration of the earlier studies, only one case of hypoglycaemia was recorded in a participant taking fasiglifam 50 mg and this highlights the low potential for fasiglifam to provoke episodes of hypoglycaemia.

The incidence of ALT ≥3 times the ULN was slightly higher in the fasiglifam groups than in the placebo group, while the incidence of ALT ≥5 times the ULN was no different between fasiglifam and placebo. The majority of participants who experienced elevation of aminotransferases had confounding factors such as hepatic steatosis and/or cholelithiasis. In some cases, however, drug-induced liver injury cannot be excluded completely. The incidence rates of other abnormal liver tests or of discontinuation of study treatment as a result of a hepatic adverse event were similar among all treatment groups. One participant treated with fasiglifam 25 mg developed a serious TEAE of abnormal hepatic function that was considered possibly drug-related by the investigator, but cholecystitis with gallstones and adenomyomatosis may have been a confounding factor in this participant. No participants treated with fasiglifam 50 mg had a serious hepatic-related TEAE. The earlier phase II studies also showed that no dose-dependent trends relating to tolerability and safety, including liver tests, were observed with doses of fasiglifam up to 200 mg once daily for 12 weeks [24,25]; however, in a recent review of data from fasiglifam global clinical trials by an independent panel of experts overseeing the clinical development programme, concerns about liver safety arose and the sponsor has voluntarily terminated the clinical development of fasiglifam [28]. The mechanisms causing the hepatic changes have not been identified so far. In contrast to most idiosyncratic drug-induced liver injuries, which commonly develop within 3 months after the initiation of a suspected drug, 3 out of 7 participants who experienced an ALT increase after the treatment with fasiglifam had a relatively long latency period in the present study, especially the 2 participants who experienced an ALT increase at the last visit during the treatment period. Although the meaning of this observation is currently unclear, further analysis using global phase III data may provide additional information for better understanding the fasiglifam drug-induced liver injury. Additional research is clearly essential to ascertain the mechanisms causing the hepatic changes and to assess whether they are potentially a class effect related to GPR40 agonism or findings specific to fasiglifam.

Whilst this phase III study was well designed in terms of controls to reduce bias and variation, the 24-week treatment period was short for a disease that will probably need life-long treatment. In addition, the number of participants treated was too small to be able to detect statistically significant differences in HbA1c between the various subgroups tested, or to detect less common TEAEs. These limitations may explain why we were not able to clearly identify any liver safety issues for fasiglifam in the present study.

In conclusion, fasiglifam is the first GPR40 agonist to undergo extensive clinical development. Fasiglifam 25 and 50 mg produced significant improvements in glycaemic control (HbA1c and FPG) with a low risk of causing hypoglycaemia in patients with type 2 diabetes inadequately controlled by diet and exercise.

Acknowledgements

K. K. is the guarantor of this work and, as such, had full access to all of 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 (Appendix S1) for their assistance with this study. The authors also thank the sponsor for assistance with data monitoring and gathering, and for funding editorial writing that was provided by Steve Clissold, Content Ed Net.

Conflict of Interest

K. E., R. N., T. O. and R. M. are employees of Takeda Pharmaceutical Company Ltd, Osaka, Japan. K. K. has received research funding, consultancy fees, or lecture fees from AstraZeneca, Boehringer-Ingelheim, Chugai, Daiichi-Sankyo, Dainippon-Sumitomo, Kowa, MSD, Novartis, Novo Nordisk, Sanofi -Aventis, Sanwa, Taisho, Takeda and Tanabe-Mitsubishi.

All authors were involved in the design of the clinical trial, interpretation of the findings and were responsible for drafting and critically revising the report, having full access to study data.

K. E., R. N., T. O. and R. M. were involved in the day-to-day management of the trial.

K. K. was the chief independent medical expert for this study, and was involved in the design of the clinical trial, interpretation of the findings and reviewed and approved the final manuscript.

This study was funded by Takeda Pharmaceutical Company Ltd. Takeda Pharmaceutical Company Ltd 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. All authors approved the final version.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. List of investigators.

Figure S1. Change in HOMA-β (%) Mean $\pm$ standard deviation (SD).

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; **13**: 4–14.
2. Sturm R. Stemming the global obesity epidemic: what can we learn from data about social and economic trends? Public Health 2008; **122**: 739–746.
3. Hill JO, Wyatt HR, Reed GW et al. Obesity and the environment: where do we go from here? Science 2003; **299**: 853–855.
4. DeFronzo RA. From the triumpherate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009; **58**: 773–795.
5. International Diabetes Federation Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation, 0000. Available from URL: http://www.idf.org/guidelines/type-2-diabetes. Accessed 22 June 2013.
6. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
7. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; **35**: 1364–1379.
8. Qaseem A, Humphrey LL, Sweet DE, on behalf of the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2012; **156**: 218–231.
9. Cryer PE. Hypoglycemia is the limiting factor in the management of diabetes. Diabetes Metab Res Rev 1999; **15**: 42–46.
10. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. Patient Educ Couns 2007; **68**: 10–15.
11. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care 1987; **10**: 617–621.
12. Arai K, Matoba K, Hirao K et al. Present status of sulfonylurea treatment for type 2 diabetes in Japan: second report of a cross-sectional survey of 15,652 patients. Endocr J 2010; **57**: 499–507.
13. Cahn A, Raz I. Emerging gliptins for type 2 diabetes. Expert Opin Emerging Drugs 2013; **18**: 245–258.
14. Pratley RE. Alogliptin: a new, highly selective dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. Expert Opin Pharmacother 2009; **10**: 503–512.
15. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. Diabet Med 1998; **15**: 297–303.
16. Leese GP, Wang J, Broomhall J et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2003; **26**: 1176–1180.
17. 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.
18. 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.
19. Bailey CJ. Could FFAR1 assist insulin secretion in type 2 diabetes? Lancet 2012; **379**: 1370–1371.
20. 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.
21. 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.
22. Leifke E, Naik H, Wu J et al. A multiple-ascending-dose study to evaluate safety, pharmacokinetics, and pharmacodynamics of a novel GPR40 agonist, TAK-875, in patients with type 2 diabetes. Clin Pharmacol Ther 2012; **92**: 29–39.
23. 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.
24. Kaku K, Araki T, Yoshinaka R. Randomized, double-blind, dose-ranging study of TAK-875, a novel GPR40 agonist, in Japanese patients with inadequately controlled type 2 diabetes. Diabetes Care 2013; **36**: 245–250.
25. Burant C, 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.
26. Kashiwagi A, Kasuga M, Araki E, for the Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society et al. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest 2012; **3**: 39–40.
27. The Japan Diabetes Society. Treatment guide for diabetes 2012–2013. 0000. Available from URL: http://www.jds.or.jp/common/fckeditor/editor/filemanager/connectors/php/transfer.php?file=/uid000025_54726561746D656E745F47756964655F666F725F44696162657465735F323031322D323031332E706466. Accessed 10 June 2014.
28. Takeda Press Release. Takeda announces termination of fasiglifam (TAK-875) development. 0000. Available from URL: www.takeda.us/newsroom/press_releasedetail.aspx?year=2013&tid=296. Accessed 10 June 2014.