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CLINICAL TRIAL

Effect of combination therapy with repaglinide and metformin hydrochloride on glycemic control in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: We investigated the efficacy and safety of repaglinide as an add-on therapy for Japanese patients with type 2 diabetes mellitus receiving metformin monotherapy (at a dose of 1,500 mg/day, mainly) in addition to diet and exercise.

Materials and methods: In the 16-week multicenter, placebo-controlled, randomized, double-blind, parallel-group trial (the phase III study), patients with type 2 diabetes mellitus with metformin monotherapy were randomly assigned to the repaglinide or placebo group. Thereafter, a 36-week, multicenter, uncontrolled, dose-titration method study was extended to a total duration of 52 weeks (the long-term study). The primary end-point of each study was a change in glycated hemoglobin (HbA_{1c}) from baseline.

Results: After 16 weeks, mean reductions in HbA_{1c} were significantly greater for the repaglinide group than for the placebo group (–0.98 ± 0.72% vs 0.13 ± 0.63%, $P < 0.001$). In the long-term study, the mean change in HbA_{1c} was –0.76 ± 0.83%. The rate of adverse events was 60.6 and 50.0% in the repaglinide and placebo groups, respectively, in the phase III study, and 78.3% in the long-term study. Hypoglycemia was reported in 11.7, 0 and 13.3% of patients in the repaglinide group, placebo group and long-term study, respectively.

Conclusions: Combination therapy with repaglinide and metformin resulted in an approximately 1% reduction in HbA_{1c} at week 16 and in a significant long-term improvement in HbA_{1c} at the end of the study. No safety problems were noted during the concomitant use of repaglinide and metformin. These studies were registered with JapicCTI (nos. JapicCTI-101202 and JapicCTI-101203).

INTRODUCTION

Repaglinide is a short-acting insulin secretagogue that is excreted into bile, and it promotes insulin secretion by a mechanism similar to sulfonylurea (SU) agents[1]. However, unlike SU agents, repaglinide is characterized by a short duration of action with transient insulin secretion because of its rapid absorption after oral administration just before a meal and early disappearance from the circulation. Thus, repaglinide reduces postprandial hyperglycemia by targeting early-phase insulin release and restoring the normal pattern of insulin secretion. Furthermore, previous studies have confirmed that repaglinide monotherapy for 16 weeks reduced glycated hemoglobin (HbA_{1c}) by 1.17%[2], and that its effect was maintained over a long period in Japanese patients with type 2 diabetes. On the basis of these results, The Ministry of Health, Labor and Welfare in Japan approved repaglinide, and it was launched in 2011.

Metformin mainly inhibits hepatic gluconeogenesis and shows a hypoglycemic effect without affecting insulin secretion

from pancreatic β-cells. It also promotes glucose uptake in peripheral tissues and controls glucose absorption in the small intestine[3]. Although metformin has long been widely used as the first-line drug for oral treatment of type 2 diabetes overseas[4,5], in Japan, the global standard dose of metformin (usually 750–1,500 mg/day, maximum dose of 2,250 mg/day) was only approved in 2010[6]. Since then, its use has increased sharply as a result of its efficacy and safety.

The combined use of repaglinide, a short-acting insulin secretagogue, and metformin, an insulin sensitizer, is complementary and expected to improve glycemic control over a long period of time without exhausting pancreatic β-cells. In fact, combined therapy with repaglinide and metformin was approved in the USA in 1997 and in Europe in 1998, and has been widely used since. However, the efficacy and safety of combination therapy with repaglinide and metformin in Japanese patients have not yet been established. Therefore, we carried out a phase III study on the combined use of metformin (at a dose of 1,500 mg/day, mainly) and repaglinide, as well as a continued long-term study, and investigated the efficacy and safety of repaglinide as an add-on therapy for Japanese patients with type 2 diabetes receiving metformin monotherapy.

METHOD

Enrolled Patients

In the phase III study, patients with type 2 diabetes were screened and enrolled if they were aged over 20 years, had received metformin monotherapy at a fixed dose (750, 1,500 or 2,250 mg/day) in addition to diet and exercise therapies in the previous 12 weeks, and had HbA$_{1c}$ of 6.9–9.4%. Patients who had been treated with insulin or a SU agent during the previous 24 weeks, or with other oral hypoglycemic agents (excluding metformin), glucagon-like peptide-1 receptor agonists or corticosteroids (oral preparation, suppository, or injection) during the previous 12 weeks were excluded. The following patients were also excluded: those with heart diseases (heart failure [New York Heart Association class III or IV]; unstable angina; myocardial infarction during the previous 12 months); diabetes complications (diabetic proliferative retinopathy or preproliferative retinopathy and serious diabetic neuropathy requiring treatment); aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) levels of >2.5-fold the upper normal limit; serum creatinine level of ≥1.3 mg/dL (males) or ≥1.2 mg/dL (females); contraindication to metformin; and malignant tumors, as well as pregnant women, possibly pregnant women and lactating women. In the long-term study, patients who completed the phase III study and voluntarily agreed to participate in the present study were enrolled.

These studies were examined and approved by the institutional review board (IRB) of each participating institution and subsequently carried out in accordance with Good Clinical Practice. At each participating institution, the investigator informed each candidate patient of the study design using the leaflet and consent form authorized by the IRB before the patient was enrolled in the study, and the patient's informed consent to the study was obtained in writing.

Study Design and Methods

The phase III study was a 16-week, multicenter, placebo-controlled, randomized, double-blind, parallel-group, comparative study. Eligible patients were randomized (2:1) to either the repaglinide or the placebo group. In each group, oral medication was given three times daily, immediately (within 10 min) before each meal, for a period of 16 weeks. On completion of the phase III study, patients were entered into a 36-week, multicenter, uncontrolled, dose-titration method study. In the phase III study, patients in the repaglinide group received repaglinide at a dose of 0.75 mg/day for the first 2 weeks and 1.5 mg/day for the following 14 weeks. Patients in the placebo group received a placebo for 16 weeks. After the phase III study, all patients who moved onto the long-term study received repaglinide at a dose of 0.75 mg/day in week 17 and 18 (initial 2 weeks of the long-term study). If no safety issues were noted, the dose was increased to 1.5 mg/day from week 19 up to week 32. The dose could be increased to 3 mg/day after week 32. A fixed dose of metformin was also administered during 52 weeks.

The primary end-point in both studies was a change in HbA$_{1c}$ at the end of the study. Secondary end-points were the proportion of patients who achieved the HbA$_{1c}$ targets of <6.9 and <6.2%, postprandial blood glucose (PPG; the area under the curve [AUC]$_{0-3 h}$ and 2-h), glycoalbumin (GA), fasting plasma glucose (FPG) and postprandial serum insulin (AUC$_{0-3 h}$). HbA$_{1c}$ (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) value and calculated using the following conversion formula: HbA$_{1c}$ (%) = 1.02 × Japan Diabetes Society (JDS) value (%) + 0.25%[7]. The meal tolerance test (approximately 400 kcal) was carried out at breakfast time at baseline and at week 16 in the phase III study, and at week 52 in the long-term study. For the meal tolerance test, breakfast was started within 30 min after the collection of blood during fasting, and the blood glucose and serum insulin levels were measured at five time-points (30, 60, 90, 120 and 180 min after the start of breakfast).

A drug-related adverse event was noted if a causal relationship with the test drug was not ruled out by the investigator. Laboratory tests (hematology, biochemistry, lactic acid and urinalysis) and the measurement of vital signs were carried out before and week 2, 4, 8, 12 and 16 after the start of treatment in the phase III study, and at week 18 and 20 and every 4 weeks from week 20 to week 52 during the long-term study. A central laboratory institute measured the data from the laboratory tests (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Twelve-lead electrocardiography (12-lead ECG) was carried out before registration in the phase III study, and at week 16, 24 and 52 after the start of treatment.

Statistical Analysis

Efficacy

In the phase III study, the differences between the repaglinide and placebo groups with regard to the changes observed in the glycemic control parameters at the end of study compared with baseline were evaluated by analysis of covariance (ANCOVA) using the baseline level as the covariate. The 95% confidence interval (two-sided) for the difference in change was also calculated. A *P*-value of <0.05 was considered statistically significant.

In the long-term study, the mean differences in changes from baseline to the end of study and 95% confidence intervals were calculated. The baseline value was set according to the treatment group in the phase III study as follows: the data obtained before the start of medication for the phase III study in the repaglinide group, and the data obtained on the first day of the long-term study in the placebo group. Descriptive statistics were calculated for measurement values and for changes from baseline at the end of study. Intragroup comparisons of HbA_{1c} were carried out by one-sample *t*-test with baseline value as control. A *P*-value of <0.05 was considered statistically significant.

The population used for analyzing efficacy evaluation – the full analysis set (FAS) – was defined as those who had at least one measurement of any efficacy parameters among the randomized patients.

Safety

The number of patients with adverse events, hypoglycemic episodes, serious adverse events and drug-related adverse events, as well as the incidence and number of events, were obtained for each treatment group.

RESULTS

The characteristics of the patients who participated in these clinical studies are shown in Figure 1. In the phase III study, 133 patients were screened and 130 patients were randomized to receive repaglinide ($n = 94$) or placebo ($n = 36$). Seven patients discontinued treatment (5 patients from the repaglinide group and 2 patients from the placebo group), and a total of 123 patients completed the phase III study: 89 in the repaglinide group and 34 in the placebo group. Two patients in the repaglinide group were excluded from the FAS analysis because of no evaluable HbA_{1c} data. Of the 123 patients that completed the phase III study, 121 patients moved onto the long-term study (87 from the repaglinide group and 34 from the placebo group). In the long-term study, one patient was excluded from the analysis because the patient was lost to follow up after the first day of the long-term study. A total of 11 patients discontinued treatment and 110 patients completed the long-term study. The repaglinide and the placebo groups in the phase III study were generally comparable with respect to demographic characteristics, diabetes duration and baseline glycemic control (Table 1). The dose of metformin was 1,500 mg/day in almost all patients.

Efficacy

The changes in glycemic control parameters in the phase III and the long-term studies are shown in Table 2. In the repaglinide group, HbA_{1c} decreased from $7.62 \pm 0.71\%$ at baseline to $6.64 \pm 0.66\%$ at the end of the phase III study. In contrast, in the placebo group, HbA_{1c} did not change significantly ($7.52 \pm 0.87\%$ vs $7.64 \pm 1.15\%$).

The mean decrease in HbA_{1c} at the end of the phase III study was $-0.98 \pm 0.72\%$ in the repaglinide group and $0.13 \pm 0.63\%$ in the placebo group. Based on ANCOVA results of the intergroup differences, the magnitude of change was significantly greater in the repaglinide group than in the placebo group, showing the superiority of repaglinide over placebo for the primary end-point ($-1.07 \pm 0.13\%$ [least square mean $\pm$ standard error], $P < 0.001$). The proportion of patients in the repaglinide group who achieved HbA_{1c} of <6.9% increased from 12.0% (11/92) at baseline to 66.3% (61/92) at the end of study; 25.0% (23/92) achieved the <6.2% target at the end of study. A subgroup analysis of HbA_{1c} response according to baseline HbA_{1c} levels showed that the treatment effect of repaglinide showed greater increases in cases with higher baseline HbA_{1c} values. No significant differences in the magnitude of change in HbA_{1c} were observed for BMI. Compared with the placebo group, the repaglinide group showed a greater reduction in PPG ($AUC_{0-3 h}$, 2-h), FPG and GA levels at the end of the study. Postprandial serum insulin $AUC_{0-3 h}$ was significantly greater in the repaglinide group than in the placebo group. In the long-term study, HbA_{1c} decreased from $7.63 \pm 0.82\%$ at the baseline to $6.87 \pm 0.84\%$ at the end of study, and the mean change was $-0.76 \pm 0.83\%$ ($P < 0.05$). HbA_{1c} decreased gradually between week 0 and 16, and remained low until week 52 (Figure 2). Consistent with the phase III study, PPG ($AUC_{0-3 h}$, 2-h), FPG, GA levels and postprandial serum insulin $AUC_{0-3 h}$ showed improvements from baseline through to week 52.

Safety

Among the 130 patients (94 in the repaglinide group and 36 in the placebo group) treated with the test drug at least once, no differences were observed in the rates of adverse event: 60.6% (57/94) in the repaglinide group and 50.0% (18/36) in the placebo group (Table 3). With regard to serious adverse events, interstitial lung disease was seen in one patient in the placebo group, but a causal relationship to the test drug was ruled out. The incidence of hypoglycemia was 11.7% (11/94) in the repaglinide group and none in the placebo group. Many of the hypoglycemic episodes in the repaglinide group were observed in the time before lunch and dinner. All of the hypoglycemic episodes were rated as mild, and there were no severe hypoglycemia episodes. In the long-term study, the adverse event rate was 78.3% (94/120). Serious adverse events occurred in eight patients. Of these patients, two died of acute myocardial infarctions or cardiorespiratory arrest. All of serious adverse events were considered unrelated to the test drug. Hypoglycemia
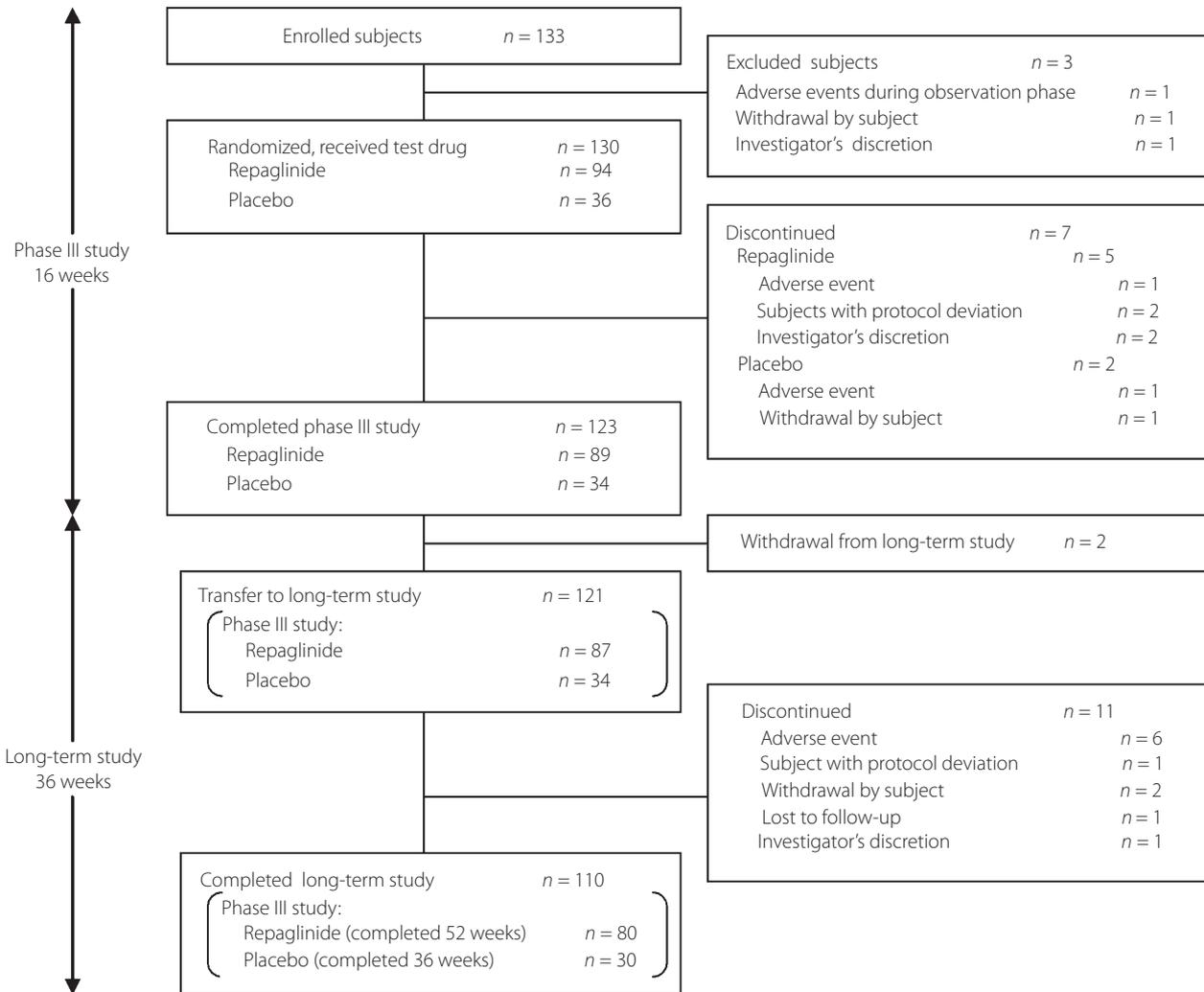
Figure 1 | Patient disposition. After randomization, patients in the phase III study received repaglinide or placebo for 16 weeks. After the phase III study, all patients who moved onto the 36-week long-term study received repaglinide.

Table 1 | Baseline characteristics of patients

	Phase III study		Long-term study ($n = 120$)
	Repaglinide ($n = 92$)	Placebo ($n = 36$)	
Sex (male/female)	61/31	21/15	79/41
Age (years)	55.1 ± 11.1	53.6 ± 12.1	54.9 ± 11.4
BMI	26.73 ± 4.04	27.28 ± 4.80	26.69 ± 4.30
Duration of diabetes (years)	7.5 ± 6.5	5.6 ± 4.7	7.1 ± 6.0
HbA_{1c} (%)	7.62 ± 0.71	7.52 ± 0.87	7.63 ± 0.82‡
$PPG\text{-}AUC_{0\text{-}3\ h}$ (mg·h/dL)	732 ± 119*	701 ± 124	719 ± 121‡
2-h PPG level (mg/dL)	251.0 ± 47.6*	239.5 ± 48.1	246.5 ± 48.4‡
FPG level (mg/dL)	168.0 ± 27.8	161.1 ± 33.1	165.3 ± 28.7‡
Postprandial serum insulin $AUC_{0\text{-}2\ h}$ (μU·h/mL)	48.50 ± 34.59*	54.71 ± 34.83†	48.36 ± 33.13§
GA (%)	20.20 ± 2.95	19.55 ± 2.80	20.18 ± 3.04‡
Metformin dose (750/1,500/2,250 mg/day)	(5/86/1)	(0/32/4)	(4/111/5)

Data are represented as n or mean ± standard deviation. *$n = 91$, †$n = 35$, ‡$n = 119$, §$n = 118$. BMI, body mass index; FPG, fasting plasma glucose; GA, glycoalbumin; HbA_{1c}, glycated hemoglobin; PPG, postprandial blood glucose.

Table 2 | Changes in glycemic control

	Phase III study								Long-term study			
	Repaglinide				Placebo							
	n	Baseline	End of study	Change from baseline	n	Baseline	End of study	Change from baseline	n	Baseline	End of study	Change from baseline
HbA1c (%)	92	7.62 ± 0.71	6.64 ± 0.66	−0.98 ± 0.72** (−1.13, −0.83)	36	7.52 ± 0.87	7.64 ± 1.15	0.13 ± 0.63 (−0.09, 0.34)	119	7.63 ± 0.82	6.87 ± 0.84	−0.76 ± 0.83 (−0.91, −0.61)
According to the baseline HbA1c (%)												
<7.4	37	6.96 ± 0.27	6.38 ± 0.41	−0.58 ± 0.45** (−0.73, −0.43)	19	6.83 ± 0.29	6.96 ± 0.57	0.13 ± 0.43 (−0.08, 0.33)	53	6.92 ± 0.30	6.51 ± 0.61	−0.41 ± 0.55 (−0.56, −0.26)
7.4 to <8.4	39	7.76 ± 0.28	6.66 ± 0.66	−1.10 ± 0.69** (−1.32, −0.87)	9	7.80 ± 0.31	7.77 ± 1.00	−0.03 ± 0.86 (−0.69, 0.63)	41	7.78 ± 0.28	7.02 ± 0.77	−0.76 ± 0.79 (−1.01, −0.51)
≥8.4	16	8.79 ± 0.32	7.16 ± 0.81	−1.63 ± 0.74** (−2.03, −1.24)	8	8.84 ± 0.32	9.14 ± 0.86	0.30 ± 0.79 (−0.36, 0.96)	25	8.91 ± 0.40	7.42 ± 1.00	−1.49 ± 0.95 (−1.88, −1.10)
According to the baseline BMI												
<25	30	7.40 ± 0.58	6.45 ± 0.58	−0.95 ± 0.79* (−1.25, −0.65)	8	7.11 ± 0.73	7.20 ± 1.01	0.09 ± 0.51 (−0.34, 0.51)	37	7.40 ± 0.67	6.58 ± 0.60	−0.82 ± 0.75 (−1.07, −0.57)
≥25	62	7.72 ± 0.74	6.72 ± 0.68	−1.00 ± 0.68** (−1.17, −0.83)	28	7.64 ± 0.88	7.77 ± 1.17	0.14 ± 0.67 (−0.12, 0.40)	82	7.74 ± 0.87	7.01 ± 0.90	−0.73 ± 0.87 (−0.92, −0.54)
PPG-AUC$_{0-3 h}$ (mg·h/dL)	88	735 ± 120	602 ± 111	−134 ± 107** (−156, −111)	33	695 ± 116	680 ± 111	−14 ± 77 (−42, 13)	110	720 ± 125	624 ± 124	−96 ± 119 (−118, −73)
2-h PPG level (mg/dL)	88	252.0 ± 48.1	201.8 ± 43.6	−50.2 ± 43.6** (−59.4, −40.9)	33	238.3 ± 45.8	234.1 ± 46.5	−4.2 ± 39.8 (−18.4, 9.9)	110	247.2 ± 49.4	208.8 ± 49.5	−38.4 ± 47.1 (−47.3, −29.5)
FPG level (mg/dL)	92	168.0 ± 27.8	138.8 ± 27.9	−29.2 ± 25.8** (−34.6, −23.9)	36	161.1 ± 33.1	157.7 ± 34.0	−3.4 ± 15.1 (−8.5, 1.7)	119	165.3 ± 28.7	146.0 ± 30.4	−19.2 ± 29.1 (−24.5, −14.0)
Postprandial serum insulin AUC$_{0-3 h}$ (μU·h/mL)	86	73.6 ± 51.1	100.1 ± 56.7	26.5 ± 27.7** (20.5, 32.4)	31	83.5 ± 53.8	77.9 ± 52.5	−5.6 ± 21.8 (−13.6, 2.4)	104	73.8 ± 51.9	93.7 ± 52.8	19.9 ± 28.9 (14.2, 25.5)
GA (%)	92	20.20 ± 2.95	16.76 ± 2.43	−3.44 ± 2.47** (−3.95, −2.93)	36	19.55 ± 2.80	19.83 ± 3.51	0.28 ± 1.80 (−0.33, 0.88)	119	20.18 ± 3.04	17.48 ± 2.58	−2.70 ± 2.63 (−3.18, −2.23)
Achievement of treatment goal at the end of the study – patients with HbA1c (%)												
<6.9	92	11 (12.0)	61 (66.3)	–	36	11 (30.6)	9 (25.0)	–	119	18 (15.1)	71 (59.7)	–
<6.2	92	0	23 (25.0)	–	36	0	1 (2.8)	–	119	1 (0.8)	21 (17.6)	–

When there was no value before the start of medication or only in the case of the value before the start of medication, the value was excluded from the evaluation. Baseline, end of study: mean ± standard deviation; change from baseline: mean ± standard deviation (95% confidence interval). Achievement of treatment goal at the end of the study – patients with glycated hemoglobin (HbA1c): n (%). *P < 0.01, **P < 0.001 (analysis of covariance for intergroup differences of the change from baseline). BMI, body mass index; FPG, fasting plasma glucose; GA, glycoalbumin; PPG, postprandial blood glucose.
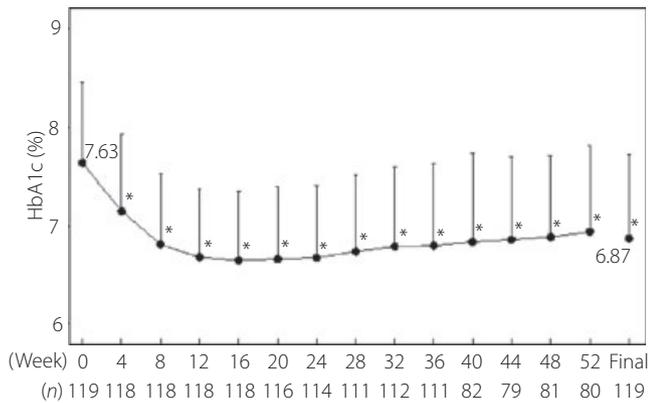
Figure 2 | Change in glycated hemoglobin (HbA$_{1c}$; mean ± standard deviation) after administration of repaglinide. *$P < 0.05$ (t-test vs baseline, not adjusted multiplicity).

occurred in 13.3% of patients (16/120). Many of the hypoglycemic episodes in the repaglinide group were observed in the time before lunch and dinner. A moderate hypoglycemic episode leading to discontinuation of the test drug was observed in one patient, and all of the other episodes were rated as mild. No severe hypoglycemia was reported. There was no clinically significant abnormal change in any laboratory parameter, lactic acid parameter, vital sign or 12-lead ECG. No lactic acidosis was noted during 52 weeks. Bodyweight increased from

72.35 ± 13.74 kg at baseline to 74.03 ± 14.03 kg at the end of the study. The incidence of adverse events did not increase during the period of administration of repaglinide.

DISCUSSION

The concomitant use of oral antidiabetic drugs with different mechanisms of action is effective in the treatment of type 2 diabetes mellitus[8]. In the present study, we investigated combination therapy with repaglinide, which stimulates early-phase insulin secretion, and metformin, which improves glycemic control by reducing hepatic glucose production and improving insulin sensitivity. The aim of the present phase III and long-term extension studies was to investigate the efficacy and safety of repaglinide as an add-on therapy in patients receiving metformin monotherapy (at a dose of 1,500 mg/day, mainly). The results of the trial confirmed that add-on therapy with repaglinide in metformin-treated patients for 16 weeks reduced HbA$_{1c}$ by approximately 1% from baseline. In addition, approximately 66% patients achieved the HbA$_{1c}$ goal of <6.9% (classified as 'excellent' or 'good') recommended by the JDS[8]. Significant improvements were also observed in PPG (AUC$_{0-3 h}$, 2-h), FPG, GA and postprandial serum insulin AUC$_{0-3 h}$. Furthermore, these beneficial effects were shown to continue for 52 weeks.

With regard to safety, hypoglycemia was the most common drug-related adverse event. However, it was not a clinically significant issue, as all hypoglycemic symptoms subsided rapidly

Table 3 | Adverse events and drug-related adverse events

	Phase III study		Long-term study (n = 120)
	Repaglinide (n = 94)	Placebo (n = 36)	
Adverse events	57 (60.6)	18 (50.0)	94 (78.3)
Deaths	0	0	2 (1.7)
Serious adverse events	0	1 (2.8)	8 (6.7)
Drug-related adverse events	19 (20.2)	2 (5.6)	33 (27.5)
Hypoglycemia	11 (11.7)	0	16 (13.3)
Most common adverse events (occurring in ≥5% of patients in any treatment group)			
Gastrointestinal disorders			
Dental caries	2 (2.1)	1 (2.8)	9 (7.5)
General disorders and administration site conditions			
Hunger	7 (7.4)	0	7 (5.8)
Infections and infestations			
Nasopharyngitis	19 (20.2)	5 (13.9)	35 (29.2)
Pharyngitis	5 (5.3)	1 (2.8)	9 (7.5)
Bronchitis	3 (3.2)	2 (5.6)	5 (4.2)
Gastroenteritis	2 (2.1)	1 (2.8)	6 (5.0)
Metabolism and nutrition disorders			
Hypoglycemia	11 (11.7)	0	16 (13.3)
Nervous system disorders			
Tremor	5 (5.3)	0	5 (4.2)
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation	1 (1.1)	3 (8.3)	4 (3.3)

Data are represented as n (%).

after measures were taken at the patient's own discretion (intake of meal, glucose or the like) or without any particular measure. Lactic acidosis, which is thought to be associated with biguanide treatment, was not observed in these studies. Taken together, these results suggest that the add-on therapy of repaglinide with the global standard dose of metformin was safe and well tolerated in Japanese patients with type 2 diabetes mellitus over a long period.

Metformin improves glycemic control without changing insulin secretion, primarily by decreasing liver glucose production and improving insulin sensitivity in peripheral tissues. Therefore, combination therapy with metformin and repaglinide would have a complementary effect. In the pancreas, postprandial insulin release from pancreatic β-cells is stimulated, whereas in the liver and peripheral tissues, glucose metabolism is increased, suggesting that this combination therapy improves glucose tolerance and is useful in the treatment of type 2 diabetes. Consistent with this theory, the results of the present study showed that combination therapy with repaglinide and metformin reduced HbA$_{1c}$ and improved PPG control with the maintenance of insulin secretion over a year.

Reports have been published on studies involving a combination treatment of metformin and various oral hypoglycemic agents in Japanese patients with type 2 diabetes mellitus. However, because of the upper limit of the metformin dose level approved in Japan, the doses used in these studies were limited to 750 mg/day or less. In a study involving the use of a combination treatment of metformin and nateglinide (one of a short-acting insulin secretagogues), the dose level of metformin was also limited to 500 or 750 mg/day[9]. In that study, HbA$_{1c}$ (JDS) decreased only slightly (7.61 ± 1.32%, at week 52) over time from the baseline level (7.75 ± 1.00%) after the start of the combination treatment[9]. In the present study, in contrast, metformin was primarily used at a dose level of 1,500 mg/day (a dose level generally used in many countries other than Japan). Therefore, it was possible, for the first time in Japan, to confirm the efficacy and safety of a combination treatment involving metformin at a dose level of 1,500 mg/day. Although an increase in the dose of metformin monotherapy from 750 mg/day to 1,500 mg/day was previously shown to further reduce HbA$_{1c}$ in Japanese type 2 diabetes mellitus patients[6], the present study showed that metformin therapy with add-on repaglinide could also reduce HbA$_{1c}$ in type 2 diabetes mellitus patients. The study allowed us to confirm that this combination therapy can help maintain low HbA$_{1c}$ for a long period of time. These results suggest that combination treatment with metformin and repaglinide is very clinically significant.

As the JDS advocates in the Guidelines for the Treatment of Diabetes Mellitus, preventing the onset and progression of complications is the major aim and challenge of diabetes management[8]. The incidence of microangiopathy was shown to be significantly associated with HbA$_{1c}$, with a higher level of HbA$_{1c}$ being a risk factor for the development of microangiopathy[10]. In addition, each 1% reduction in HbA$_{1c}$ has been shown to result in a 37% decrease in the risk of microvascular complications[11]. When HbA$_{1c}$ was below 6.9%, the onset and progression of microangiopathy was found to be almost completely prevented[12]. Furthermore, a previous study showed a continuously increasing risk of the onset and prevalence of microvascular complications with increasing FPG[12]. Postprandial hyperglycemia was also associated with an increasing risk of macrovascular disease[13–16], and was identified as an independent risk factor for macrovascular disease[15]. From these observations, repaglinide and metformin combination therapy can be expected to not only provide good glycemic control, such as reductions in HbA$_{1c}$ and postprandial blood glucose, but also to prevent the onset and progression of micro- and macrovascular complications.

In conclusion the present findings show that combination therapy with repaglinide and metformin can be an effective treatment option for the management of Japanese type 2 diabetes patients.

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