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BRIEF REPORT

Efficacy and safety of pemafibrate in people with type 2 diabetes and elevated triglyceride levels: 52-week data from the PROVIDE study

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The aim of this study was to evaluate the efficacy and safety of pemafibrate in people with type 2 diabetes and hypertriglyceridaemia over a 52-week period. Participants were randomly assigned to receive treatment with placebo or pemafibrate at a dose of 0.2 or 0.4 mg/d for 24 weeks (treatment period 1). The main results from treatment period 1 have been reported previously. The assigned treatment was continued up to week 52, except that the placebo was changed to pemafibrate 0.2 mg/d after week 24 (treatment period 2). The percentage changes in fasting serum triglyceride (TG) levels at week 52 (last observation carried forward) were −48.2%, −42.3%, and −46.4% in the placebo/pemafibrate 0.2 mg/d (n = 57), pemafibrate 0.2 mg/d (n = 54), and pemafibrate 0.4 mg/d (n = 55) groups, respectively. Levels of TG, non-HDL cholesterol and total cholesterol stably decreased, whereas levels of HDL cholesterol increased with pemafibrate treatments over 52 weeks. Pemafibrate was well tolerated throughout the study period. The present study is the first to show that pemafibrate treatment substantially ameliorated lipid abnormalities and was well tolerated for 52 weeks in people with type 2 diabetes and hypertriglyceridaemia.

KEYWORDS
clinical trial, dyslipidaemia, lipid-lowering therapy, phase III study, randomized trial, type 2 diabetes

1 | INTRODUCTION

Characteristic lipid abnormalities, such as high triglyceride (TG), low HDL cholesterol, and increased small dense LDL cholesterol levels, typically attributed to insulin resistance, are complications often noted in people with type 2 diabetes.[1] Peroxisome proliferator-activated receptor-α (PPARα) agonists, such as fibrates, are highly effective in treating these lipid abnormalities.[2] Pemafibrate, a novel selective PPARα modulator (SPPARMα), has potent TG-lowering and HDL cholesterol-increasing activities, almost no effect on serum creatinine levels, and an ameliorating effect on liver function test values.[3] Furthermore, it has high efficacy at low doses and is safe for clinical use, similarly to placebo.[4–7]

The aim of the present phase III trial was to evaluate the efficacy and safety of pemafibrate compared to placebo during the first 24-week period (treatment period 1). After treatment period 1, treatment period 2 was initiated, from week 24 to week 52, with the placebo changed to 0.2 mg/d pemafibrate. The main results from treatment period 1 have been reported previously.[6] This report summarizes the results including treatment period 2, which spanned 52 weeks. Furthermore, the efficacy and safety of pemafibrate in combination with and without statins were also investigated.

2 | METHODS

The PROVIDE study (pemafibrate study to validate a 52-week efficacy and safety in people with type 2 diabetes comorbid with elevated triglyceride levels) was a multicentre, placebo-controlled, randomized, double-blind, parallel-group study. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Ministerial Ordinance on Good Clinical Practice for Drugs issued by the Ministry of the Health and Welfare, Japan. The study protocol was approved by the institutional review boards of all the 34 sites. Written informed consent was obtained from all participants before their inclusion in the study.

The study methods have been reported previously.[6] Briefly, patients with type 2 diabetes and hypertriglyceridemia (TG levels ≥150 mg/dL [1.7 mmol/L] and ≤1000 mg/dL [11.3 mmol/L]) were treated with placebo or pemafibrate at a dose of 0.2 or 0.4 mg/d (twice daily) for 24 weeks. After week 24, placebo was changed to pemafibrate 0.2 mg/d (placebo/pemafibrate 0.2 mg/d group), and treatment in the pemafibrate 0.2 mg/d and 0.4 mg/d groups was continued unchanged up to week 52 (Figure S1). A meal tolerance test was performed at weeks 0, 24 and 52 at facilities where the test was feasible.

The primary efficacy and safety endpoints were the percentage change in fasting serum TG levels and the incidence of adverse events (AEs) and adverse drug reactions (ADRs), respectively. Additional information can be found in Appendix S1.

3 | RESULTS

Figure S2 shows the disposition of participants. Participant characteristics have been reported previously.[6]

The percentage changes in fasting serum TG levels at week 52 (last observation carried forward [LOCF]) were −48.2%, −42.3% and −46.4% in the placebo/pemafibrate 0.2 mg/d, pemafibrate 0.2 mg/d and pemafibrate 0.4 mg/d groups, respectively. TG, HDL cholesterol, non-HDL cholesterol and total cholesterol levels stably improved in the pemafibrate groups over the 52-week period (Figures 1 and S3). Similar findings were observed for remnant lipoprotein cholesterol and other apolipoprotein (Apo) levels (Table S1). Results of the meal tolerance test at week 52 were similar to those at week 24 (Figure S4).

The effects of pemafibrate on glucose metabolism were variable (Figures 1 and S3). Fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) decreased after switching from placebo to pemafibrate 0.2 mg/d at week 24. This trend was also observed at the start of pemafibrate administration in treatment period 1. Glycoalbumin levels tended to increase in treatment period 2, only in the pemafibrate 0.2 mg/d group. Glycated haemoglobin (HbA1c) levels increased over time in all groups. Pemafibrate did not have a major effect on the postprandial plasma glucose and insulin levels (Figure S4).

The incidence of AEs was 81.8%, 77.8% and 78.2% for the placebo/pemafibrate 0.2 mg/d (excluding the events during treatment period 1), pemafibrate 0.2 mg/d and pemafibrate 0.4 mg/d groups, respectively (Table 1). During the 52-week period, no duration-dependent treatment effect was noted on the incidence of AEs or ADRs (Table S2). Serious AEs occurred after pemafibrate treatment, with 21 episodes in 16 participants. A causal relationship with the study treatment was ruled out in all cases, apart from the possible development of a bile duct stone in one participant in the pemafibrate 0.2 mg/d group. There were 12 episodes of AEs that led to discontinuation of the study treatment in 12 participants. Causal relationships with the study treatment could not be ruled out for the eczema AE observed in the placebo/pemafibrate 0.2 mg/d group, bile duct stone in the pemafibrate 0.2 mg/d group, and acute renal failure and liver dysfunction in the pemafibrate 0.4 mg/d group.

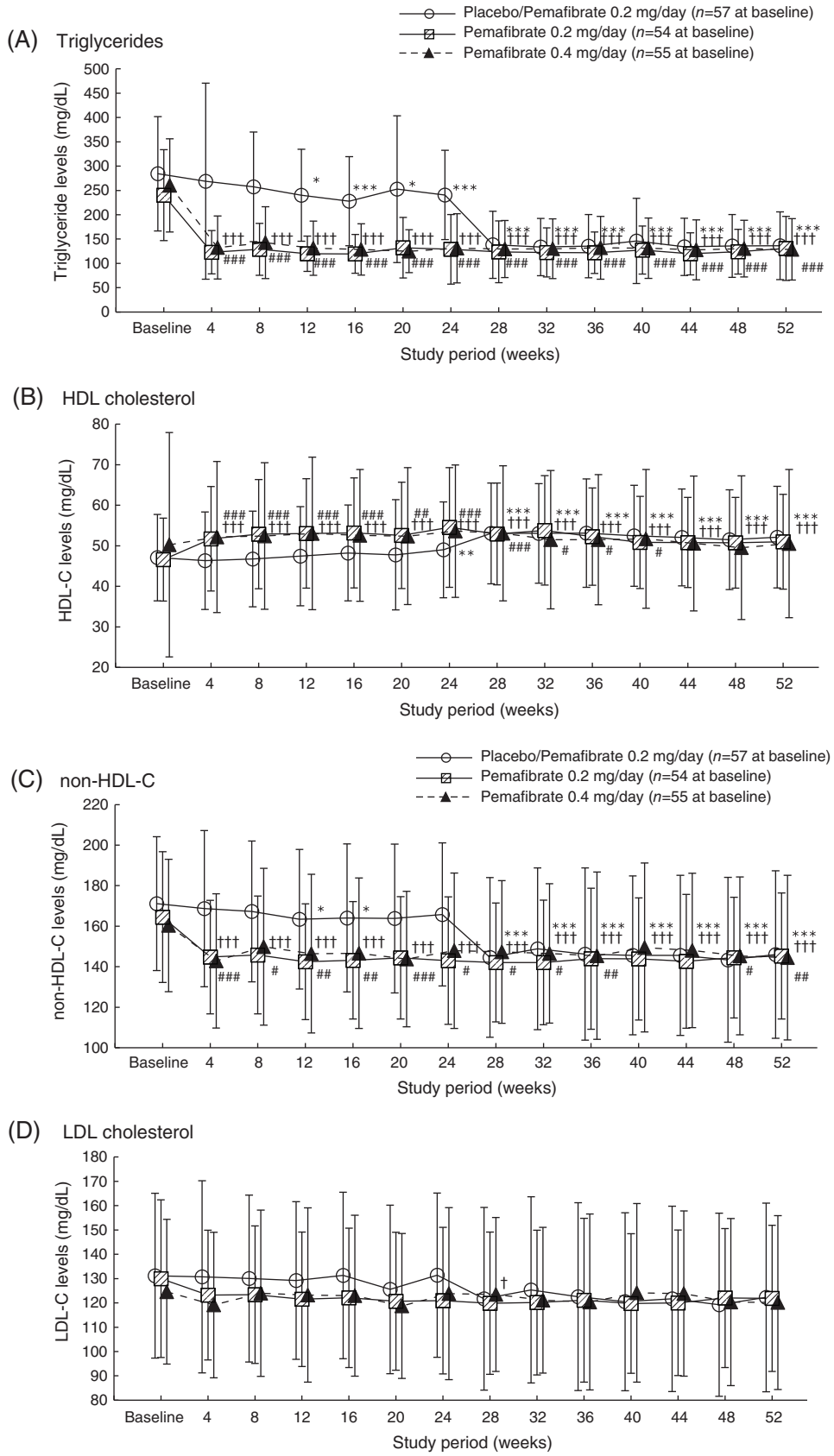

FIGURE 1 **A–H,** Lipids and levels of glucose-related variables over 52 weeks. Values are presented as mean ± SD. **P* <0.05, ***P* <0.01, ****P* <0.001 vs. baseline for placebo/pemafibrate 0.2 mg/d (one-sample *t*-test). †*P* <0.05, ††*P* <0.01, †††*P* <0.001 vs. baseline for pemafibrate 0.2 mg/d (one-sample *t*-test). #*P* <0.05, ##*P* <0.01, ###*P* <0.001 vs. baseline for pemafibrate 0.4 mg/d (one-sample *t*-test). FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance

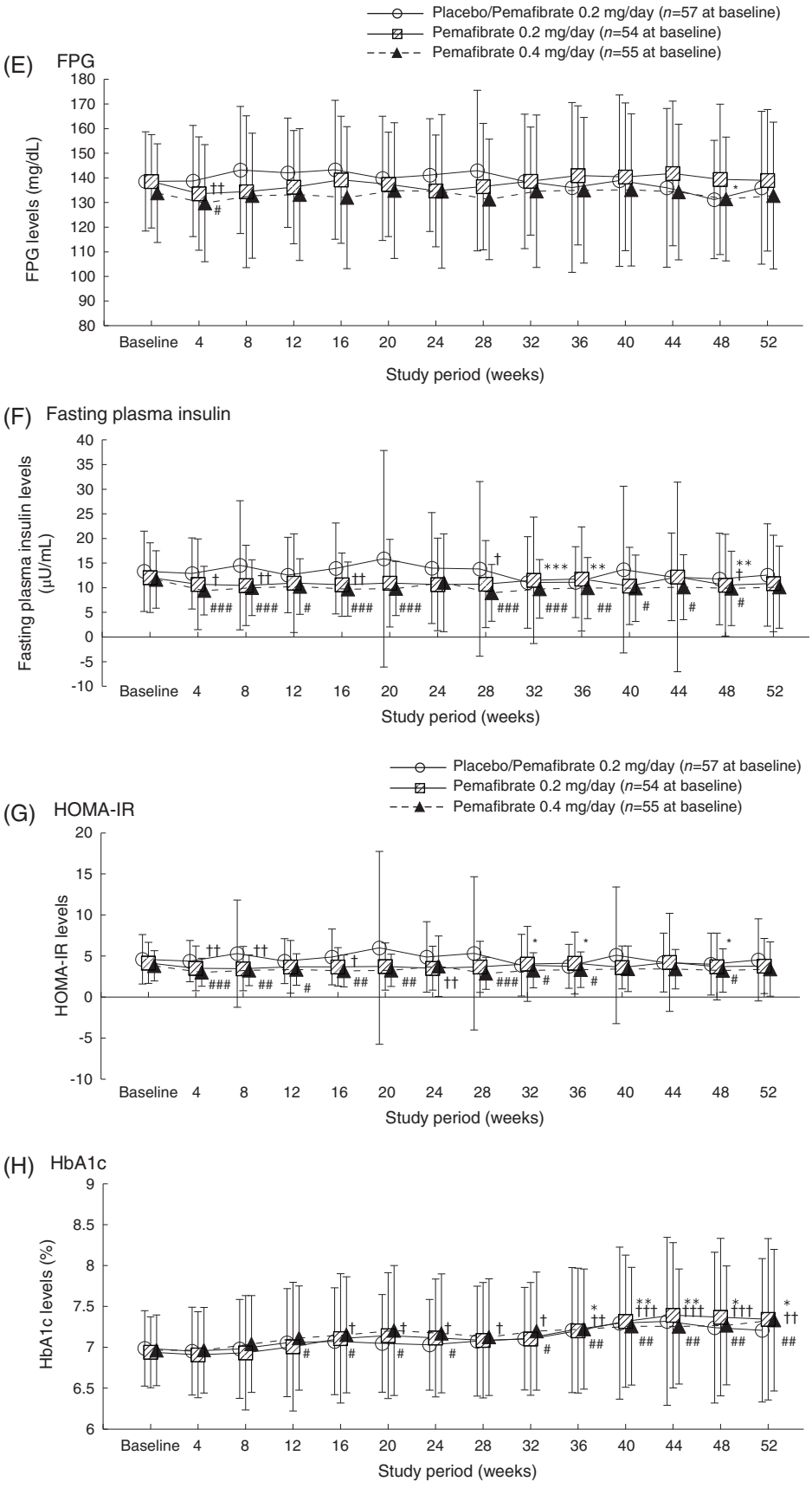

FIGURE 1 Continued

TABLE 1 Summary of adverse events and adverse drug reactions occurring throughout the study period

	Placebo/Pemafibrate 0.2 mg/d	Pemafibrate 0.2 mg/d	Pemafibrate 0.4 mg/d
	Treatment period 2[a]	Treatment period 1 + 2	Treatment period 1 + 2
	(n = 55)	(n = 54)	(n = 55)
Total AEs	45 (81.8)	42 (77.8)	43 (78.2)
Serious AEs	6 (10.9)	6 (11.1)	4 (7.3)
AEs leading to discontinuation	4 (7.3)	3 (5.6)	5 (9.1)
Total ADRs	12 (21.8)	11 (20.4)	15 (27.3)
Serious ADRs	0	1 (1.9)	0
ADRs leading to discontinuation	1 (1.8)	1 (1.9)	2 (3.6)
Laboratory tests			
AST >3 × ULN	0	2 (3.7)	0
AST >5 × ULN	0	1 (1.9)	0
ALT >3 × ULN	1 (1.8)	0	0
ALT >5 × ULN	0	0	0
GGT >3 × ULN	2 (3.6)	3 (5.6)	0
GGT >5 × ULN	0	1 (1.9)	0
Creatine kinase >4 × ULN	1 (1.8)	1 (1.9)	0
Creatine kinase >5 × ULN	1 (1.8)	1 (1.9)	0
Creatine kinase >10 × ULN	0	0	0
Serum creatinine >1.5 mg/dL (132.6 μmol/L)	2 (3.6)	2 (3.7)	2 (3.6)
Serum creatinine >2.0 mg/dL (176.8 μmol/L)	1 (1.8)	1 (1.9)	1 (1.8)
Serum creatinine >1.5 × baseline	2 (3.6)	1 (1.9)	1 (1.8)
Serum creatinine >2.0 × baseline	0	0	0

Abbreviations: ADR, adverse drug reaction; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.
Data are presented as number of participants (%).
[a]Excluding the events occurring in the placebo group during treatment period 1.

Alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) levels decreased after pemafibrate treatment for 52 weeks. Serum creatinine level increased and estimated glomerular filtration rate decreased slightly (Figure S5). No noteworthy findings were found with respect to increased levels above the cut-off values of aspartate aminotransferase (AST), ALT, GGT, creatine kinase and serum creatinine, and no participant in the pemafibrate 0.4 mg/d group had increased levels of these, excluding serum creatinine (Table 1).

The incidence of AEs in the pemafibrate groups showed no significant difference from that in the placebo group, in participants with and without statin therapy (Table S3). Regardless of concomitant statin therapy, significant decreases in TG, remnant lipoprotein cholesterol, ApoB48, ApoCII, ApoCIII, ApoCIII/ApoCII and ApoE, and significant increases in ApoAII were observed in the pemafibrate groups compared with the placebo group at week 24 (LOCF; Figures S6 and S7). The effects of pemafibrate on glycaemic and safety variables were also similar between statin and no statin treatment (Figures S8 and S9).

4 | DISCUSSION

This is the first study to evaluate the efficacy and safety of pemafibrate in people with type 2 diabetes and hypertriglyceridaemia for a 52-week period.

Pemafibrate significantly improved lipid abnormalities accompanying type 2 diabetes, including high TG-rich lipoprotein and low HDL cholesterol levels for a long-term period of up to 52 weeks. Moreover, the effect of pemafibrate on lipid abnormalities was similar for statin and for no statin treatment. The efficacy of pemafibrate on lipid profiles seems to be similar for both 0.2 mg/d and 0.4 mg/d; however, in the pooled analyses of six placebo-controlled trials with pemafibrate, pemafibrate 0.4 mg/d lowered TG-rich lipoproteins, ApoCIII, fasting plasma glucose, insulin, GGT and ALP to a greater extent than pemafibrate 0.2 mg/d.[8,9] Cholesterol content in small-sized HDL, which is thought to be more anti-atherogenic, increased to a greater degree when treated with pemafibrate 0.4 mg/d than with pemafibrate 0.2 mg/d.[6] Based on the above results, pemafibrate 0.4 mg/d seems to be more efficient in reducing atherosclerotic cardiovascular disease than pemafibrate 0.2 mg/d. This appropriate higher dose of pemafibrate (0.4 mg/d) has been used in the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study, evaluating the effects of pemafibrate on the prevention of cardiovascular diseases in combination with statin.[10]

Changes in serum creatinine levels with placebo, pemafibrate 0.2 mg/d, and pemafibrate 0.4 mg/d after 24 weeks were −0.013 mg/dL (−1.15 μmol/L), 0.026 mg/dL (2.30 μmol/L), and 0.031 mg/dL (2.74 μmol/L), respectively. Changes in serum creatinine levels with pemafibrate treatment were smaller than with fenofibrate treatment in the ACCORD lipid study[11] (a ∼0.2-mg/dL increase in the fenofibrate group and

~0.02-mg/dL increase in the placebo group at month 12 from 0.9 ± 0.2 mg/dL at baseline). The FIRST study[12] showed that, in the fenofibric acid group during the 104-week treatment period, 2.7% of participants had a serum creatinine level >2.0 mg/dL and 20.7% and 2.1% of participants had a 1.5-fold and 2-fold increase from baseline, respectively, with these percentages being higher than those in the placebo group. Previous studies comparing the effects of pemafibrate with those of fenofibrate showed that pemafibrate had a smaller effect than fenofibrate on serum creatinine levels,[4,7,13] which was also confirmed during our long-term treatment of 52 weeks in people with type 2 diabetes (Table 1).

Pemafibrate is a SPPARMα, which has been developed from the concept that PPARα agonists could trigger different biological responses via the same receptor and that their benefits could be separated from their unwanted side effects.[3] The expression of several PPARα target genes differed under treatment with pemafibrate and fenofibrate.[14] Although further investigation is needed to justify the difference in the clinical profile of pemafibrate from that of other fibrates, pemafibrate is reported to have a good benefit–risk balance. Pemafibrate had a TG-lowering effect equal to or greater than that of fenofibrate, but the rates of AEs in the pemafibrate group were lower than those in the fenofibrate group.[7,13] Furthermore, pemafibrate, but not fenofibrate, decreased ALT and GGT levels. A phase II trial of pemafibrate in patients with non-alcoholic fatty liver disease is ongoing (ClinicalTrials.gov Identifier: NCT03350165).

Throughout the study period of the present study, the dosage regimen of antidiabetic agents was changed in 22 participants. The effect of pemafibrate on glucose metabolism was not affected after excluding these 22 participants (Figures S10 and S11). Pemafibrate did not affect body weight during the 52-week treatment period, although body weight significantly decreased at several timepoints. There were no specific trends in seasonal variability in glucose metabolism under pemafibrate treatment (data not shown).

The reason for the significant increase in HbA1c after 12 weeks of treatment is unclear, considering no remarkable changes in fasting plasma glucose, postprandial glucose or glycoalbumin levels were observed. The increase in HbA1c could be attributable to time-dependent changes observed in people with diabetes or possibly a false increase. Fibrates improved red blood cell deformability by modifying erythrocyte membrane lipids,[15] which might affect erythrocyte dynamics and lifespans, as well as HbA1c levels. Pemafibrate treatment led to a decrease in fasting plasma glucose, fasting insulin levels and HOMA-IR during treatment period 1 in the previous study,[6] and showed a significant increase in splanchnic glucose uptake rates, evaluated using the hyperinsulinaemic-euglycaemic clamp study,[16] suggesting that pemafibrate improves glucose metabolism, although the effects were limited.

The present study has several limitations. First, it included people with type 2 diabetes of relatively short duration, who were administered fewer combined antidiabetic agents. Further evidence and clinical experience in real-world settings are therefore necessary to establish the efficacy and safety of pemafibrate. Second, the study participants were all Japanese, therefore, the generalizability of the results of this study to other ethnicities is unclear. Third, a placebo control was not used from week 24 to week 52, therefore, the efficacy and safety of pemafibrate during the 52-week treatment should be assessed carefully.

In conclusion, the efficacy and safety of pemafibrate in people with type 2 diabetes with hypertriglyceridaemia noted during the previous 24-week placebo-controlled period were sustained over 52 weeks. Pemafibrate rarely had unfavourable effects on liver and renal function test results, even in participants with type 2 diabetes.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

E.A., S.Y., H.A., K.Y., J.S., T.I., J.N., H.M., N.Y., Y.T., H.W., H.S. and S.I. contributed to the concept, design and execution of the study, and to the interpretation of the data. E.A. substantially contributed to writing and critically review of the manuscript. S.Y., H.A., K.Y., J.S., T.I., J.N., H.M., N.Y., Y.T., H.W. and S.I. contributed to critically reviewing the manuscript. H.S. 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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