Study protocol of the PROUD48 study comparing the effects of pemafibrate and omega-3 fatty acid ethyl esters on ApoB-48 in statin-treated patients with dyslipidaemia: a prospective, multicentre, open-label, randomised, parallel group trial in Japan

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ABSTRACT

Introduction This study will compare the lowering effects of pemafibrate and omega-3 fatty acid ethyl esters on fasting apolipoprotein B-48 (apoB-48), a surrogate marker reflecting postprandial hypertriglyceridaemia, which is a residual risk for atherosclerotic cardiovascular disease with statin treatment.

Methods and analysis This is a prospective, multicentre, open-label, randomised, parallel group, comparative trial. Adult Japanese patients with dyslipidaemia receiving statin treatment for more than 4 weeks with a fasting triglyceride level ≥177 mg/dL will be randomly assigned in a 1:1 ratio to receive pemafibrate (0.4 mg orally per day) or omega-3 fatty acid ethyl esters (4 g orally per day) for 16 weeks. The primary endpoint is the percentage change in fasting apoB-48 from baseline to 16 weeks. The key secondary endpoints include the change in fasting apoB-48 from baseline to 16 weeks, the percentage changes in clinical variables from baseline to 16 weeks and the incidence of adverse events. A total sample size of 128 was set by considering the increased dropout rate due to the COVID-19 pandemic, in addition to estimation based on a two-sided alpha of 0.05 and a power of 0.8 for apoB-48.

Ethics and dissemination The study protocol has been approved by the Certified Review Board of the University of the Ryukyus for Clinical Research Ethics (No. CRB7200001) and will be performed in accordance with the Declaration of Helsinki. Written informed consent will be obtained from all participants. The results of the study will be disseminated through publications and conference presentations to participants, healthcare professionals and the public.

Trial registration number JRCTs071200011.

INTRODUCTION

Increasing numbers of patients with atherosclerotic cardiovascular disease (ASCVD), such as coronary artery disease (CAD) and stroke, and the increased mortality associated with ASCVD, have become global public health issues. The prevention and treatment of ASCVD require comprehensive management of various cardiovascular risk factors, including dyslipidaemia, hypertension, diabetes mellitus, obesity and smoking. Lipid management is especially important for preventing and treating ASCVD. A reduction of 1 mmol/L in low-density lipoprotein cholesterol (LDL-C) with statin therapy is associated with a 25% lower incidence of major vascular events in individuals without prior ASCVD. The remaining >70% incidence rate represents the residual risk of ASCVD, which has unmet medical needs in lipid management. The residual ASCVD...
risks includes increased triglyceride (TG) and decreased high-density lipoprotein cholesterol (HDL-C) levels.\textsuperscript{2-6} The assessment of hypertriglyceridaemia as a predictor of ASCVD is more useful in a non-fasting state than in a fasting state.\textsuperscript{3,4,7-10} TG-rich lipoproteins (TRLs), represented by chylomicron remnants, increase with dietary intake and are thought to be the main cause of increased postprandial TGs and to evoke atherosclerosis by deposition on the arterial intima.\textsuperscript{11} TRLs are also independent risk factors for ASCVD.\textsuperscript{12,13}

Fibrates and polyunsaturated fatty acids (PUFAs) are important pharmacotherapeutic agents for hypertriglyceridaemia. Fibrates are primarily peroxisome proliferator-activated receptor \(\alpha\) (PPAR\(\alpha\)) agonists, and are associated with both decreases in TGs and increases in HDL-C.\textsuperscript{14} In a meta-analysis, Jun \textit{et al.}\textsuperscript{15} showed that fibrates reduced the risk of major cardiovascular events, predominantly by preventing coronary events. Pemafibrate, a selective PPAR\(\alpha\) modulator, has recently been made available as a new TG-lowering drug. Pemafibrate has not only higher PPAR\(\alpha\) selectivity but also the same or better TRL-lowering effects than conventional fibrates and is associated with fewer adverse events.\textsuperscript{16,17} Furthermore, a study to verify its efficacy and safety when administered in combination with statins showed that the frequencies of adverse events and adverse drug reactions with pemafibrate treatment were similar to those with placebo treatment.\textsuperscript{18} Therefore, pemafibrate is now expected to become a new therapeutic agent for increased TGs and decreased HDL-C. The PUFA omega-3 fatty acid ethyl ester (Omega-3) has a TG-lowering effect by suppressing very-low-density lipoprotein synthesis in the liver and has a slight HDL-C-increasing effect. Treatment with eicosapentaenoic acid (EPA) in combination with statins has been reported to reduce the ASCVD risk, including cardiovascular death\textsuperscript{19} and CAD incidence.\textsuperscript{20} Although EPA and docosahexaenoic acid (DHA) (EPA/DHA) are also expected to lower the ASCVD risk under statin treatment, the STRENGTH trial examining the effects of high-dose EPA/DHA on cardiovascular outcomes failed to show a reduction in major adverse cardiovascular events (MACE).\textsuperscript{21} In addition, no benefits of EPA/DHA for cardiovascular events were observed in the ASCEND trial or the ORIGIN trial conducted with participants including those taking statins.\textsuperscript{22,23} Therefore, the protective effects of n-3 PUFAs on cardiovascular events have not yet been fully confirmed. Pemafibrate and omega-3 should both have antiatherosclerotic effects as therapeutic agents for hypertriglyceridaemia; however, the differences in the lowering effects of the two agents on TRLs remain to be elucidated.

Apolipoprotein B-48 (apoB-48) is synthesised in the intestine.\textsuperscript{24} Masuda \textit{et al.}\textsuperscript{25} reported that fasting apoB-48 levels were significantly correlated with the incremental area under the curve (AUC) of TGs after the ingestion of a high-fat meal, indicating that the fasting apoB-48 level is a useful marker for postprandial hypertriglyceridaemia. Furthermore, the fasting apoB-48 level is correlated with the prevalence of CAD\textsuperscript{26} and carotid intima–media thickness (IMT),\textsuperscript{27} and is considered a useful marker for ASCVD risk.

To reduce the residual risk for ASCVD under statin treatment, new evidence is required to provide pharmacotherapeutic options for postprandial hypertriglyceridaemia. Among the treatment options, pemafibrate, rather than conventional fibrates and omega-3, is expected to be an effective therapeutic agent. However, the differences in efficacy for postprandial hypertriglyceridaemia between these drugs have not been verified.

Therefore, in this prospective, multicentre, open-label, randomised, parallel group trial we will compare the lowering effects of pemafibrate and omega-3 on fasting apoB-48 levels, a marker that reflects postprandial hypertriglyceridaemia, which is one of the residual risk factors for ASCVD with statin treatment.

**METHODS AND ANALYSIS**

**Study design**

The Pemafibrate Reduction of TRLs with Omega-3 for Unmet needs in Dyslipidaemic patients on target to apoB-48 study is a prospective, multicentre, open-label, randomised, parallel group, comparative study to compare the effects of pemafibrate and omega-3 on the fasting apoB-48 level, a surrogate marker for postprandial hypertriglyceridaemia, in patients with dyslipidaemia.

**Study participants**

This study will enrol Japanese patients with dyslipidaemia in accordance with the principles of the Declaration of Helsinki and its amendments. The participants will be ambulatory patients with dyslipidaemia attending Asahikawa Medical University Hospital (Asahikawa, Hokkaido, Japan), Caress Sapporo Hokko Memorial Clinic (Sapporo, Hokkaido, Japan), Hirumitsu Heart Clinic (Nagoya, Aichi, Japan) and Keiyukai Yoshida Hospital (Asahikawa, Hokkaido, Japan). Informed consent for participation will be obtained from all participants after the investigators have explained the study in full. Table 1 shows the inclusion and exclusion criteria for participation. The fasting TG level of ≥177 mg/dL in the inclusion criteria was set according to the fasting TG level of ≥150 mg/dL in the diagnostic criteria for dyslipidaemia in the guidelines of the Japan Atherosclerosis Society\textsuperscript{28} and considering the non-fasting TG level of ≥2 mmol/L in the joint consensus statement of the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine.\textsuperscript{29} The fasting TG level of ≥500 mg/dL (5.7 mmol/L) in the inclusion criteria was based on the levels generally regarded as indicating severe hypertriglyceridaemia.\textsuperscript{30} We adopted a serum creatinine level ≥1.5 mg/dL as the exclusion criterion for renal dysfunction, which is described in the package insert of pemafibrate as a criterion for patients with renal impairment requiring careful administration.
Randomisation and intervention

Enrolment and randomisation will be done centrally using an electronic data capture (EDC) system. After providing consent and enrolment, the participants will be assigned randomly to the pemafibrate or omega-3 treatment groups in a 1:1 ratio (figure 1). This randomised assignment will be stratified based on three factors: fasting TG level (< 300 or ≥ 300 mg/dL), sex (male or female) and age (< 65 or ≥ 65 years). Participants allocated to the pemafibrate group will be given pemafibrate at a dose of 0.2 mg orally two times per day for 16 weeks, with continuing statin treatment. Participants allocated to the omega-3 group will be given Omega-3 at a dose of 2 g orally two times per day for 16 weeks, with continuing statin treatment. In principle, the addition of new drugs, discontinuation or dose changes of all drugs, including statins, pemafibrate and omega-3, will not be permitted during the study. Drugs that are contraindicated for coadministration with pemafibrate or omega-3 are cyclosporine and rifampicin (for pemafibrate). Drugs that should be prohibited for use during the study due to the nature of the trial are insulin, fibrates, EPA, proprotein convertase subtilisin/kexin type 9 inhibitors and microsomal TG transfer protein inhibitors. All participants will be on a diet with an optimised total energy intake based on their ideal body weight and daily activity to maintain an appropriate body weight during the study based on Japan Atherosclerosis Society guidelines.28

Primary and secondary endpoints

The primary endpoint of this study is the percentage change in fasting apoB-48 level from baseline to 16 weeks. The key secondary endpoints include the change in fasting apoB-48 from baseline to 16 weeks, the percentage changes in clinical variables from baseline to 16 weeks and the incidences of adverse events and diseases. Other secondary endpoints include the changes in clinical variables from baseline to 16 weeks and the relationship between fasting apoB-48 level and clinical variables at 16 weeks. The clinical variables include parameters related to lipids and atherosclerosis (remnant lipoprotein
cholesterol, small dense LDL-C, total cholesterol, TGs, LDL-C, HDL-C, apoA-I, apoA-II, ApoB, apoC-III, apoE and lipoprotein subfractions), parameters related to glycaemic control (fasting plasma glucose, fasting immunoreactive insulin (IRI), homeostasis model assessment insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) and glycated haemoglobin A1c (HbA1c)), blood biochemical parameters (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatinine, estimated glomerular filtration rate and creatine kinase), fibrinogen, physical findings (blood pressure, body weight, body mass index (BMI) and waist circumference) and other examinations (lean mass, fat mass, muscle mass, liver to spleen ratio and visceral fat area).

**Data management**

Clinical data will be managed with anonymised study-specific identification numbers using an EDC system. The data will be managed by an independent data centre (Nexis, Fukuoka, Japan), including entry, coding, security, storage and cleaning. Investigators and the head of each institution will archive the information related to the study for 5 years from the date of study completion. The data centre will also archive the information related to this study, including electronic media, on the EDC system.

**Safety evaluations and adverse events**

All adverse medical events that occur in the participants, including exacerbations of pre-existing diseases, will be treated as ‘adverse events’ during the study. Exacerbations of comorbidities at baseline will also be treated as adverse events. Any diseases, disorders, deaths and infectious diseases suspected to have been caused by the implementation of this study will be treated as ‘diseases’. If adverse events or diseases are found, the investigators will immediately offer appropriate treatment, report to

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**Table 2** Observation items and study schedule

| Observation items                      | Registration | Treatment period | Discontinuation |
|----------------------------------------|-------------|-----------------|----------------|
| Informed consent                       | o           |                 |                |
| Eligibility                            | o           |                 |                |
| Patient characteristics                | o           |                 |                |
| Drug adherence                         | o           | o              | o             |
| ApoB-48                                | o           |                 |                |
| Remnant lipoprotein cholesterol        | o           |                 |                |
| Small dense LDL                        | o           |                 |                |
| Lipids                                 | o           |                 |                |
| Lipoprotein subfractions               | o           | o              | o             |
| Apolipoprotein                         | o           |                 |                |
| Biochemical parameters                 | o           | o              | o             |
| Plasma glucose                         | o           |                 |                |
| IRI and glycated haemoglobin A1c      | o           |                 |                |
| Fibrinogen                             |             | o              |                |
| Height                                 | o           |                 |                |
| Physical examinations                  | o           | o              |                |
| Other examinations                     |             | o              |                |
| Adverse events and diseases            |             |                 |                |

Physical examinations include blood pressure, body weight, body mass index (BMI) and waist circumference. Other examinations include lean mass, fat mass, muscle mass, liver to spleen ratio and visceral fat area.

White circles, required items.

Solid circles, optional items.

ApoB-48, apolipoprotein B-48; IRI, immunoreactive insulin; LDL, low-density lipoprotein.
the principal investigator and the head of each institution and record the information in the medical record, case report form and EDG system.

**Data and safety monitoring**

This study will be monitored by an independent data and safety monitoring board belonging to Asahikawa Medical University. The board principally fulfils the following roles: preparation of monitoring plan; implementation of central monitoring before, during and after the study; acquisition of data from the independent data centre and report to the principal investigator in the event of safety concerns regarding study participants or the study is considered to not be scientific. The main items to be validated in monitoring are as follows: approval status of the Certified Review Board of the University of the Ryukyus for Clinical Research Ethics, study progress status, case report form submission status, case registration status, occurrence of adverse events and bias of the data employed as allocation factors between the two groups.

An audit of the study will be conducted by an independent auditor selecting one institution and according to the following schedules: about 2 months after the third visit (at 16 weeks) of the 10th case of the institution and at the end of the study. The audit report will be submitted to the principal investigator and the head of the institution where the audit was conducted.

**Compensation**

If participants involved in the study have any health hazards, the principal investigator and each institution will provide medical care and pay compensation from the clinical trial insurance (if participants are eligible for payment).

**Sample size**

This study will compare the lowering effects of pemafibrate and omega-3 on the percentage change in fasting apoB-48 level from baseline to 16 weeks. The percentage changes in fasting apoB-48 level on treatment with pemafibrate at 0.4 mg/day or omega-3 at 4 g/day combined with a statin were reported previously to be $-57.3\% \pm 24.2\%$ and $-22.0\%$, respectively. We used $58.2\%$ as the SD for our original estimation.

No interim analysis will be performed in this study. The primary and secondary endpoints except for adverse events will be analysed primarily using the full analysis set (FAS) and secondary per-protocol set (PPS). The FAS includes participants enrolled in this study and assigned to treatment groups, excluding those with major study protocol violations, such as failing to obtain consent or enrolment outside the study period. The PPS includes participants from the FAS after excluding those who violated the inclusion or exclusion criteria, used drugs contraindicated for pemafibrate and omega-3 or adhered poorly to pemafibrate and omega-3 ($<75\%$ or $\geq 120\%$) during the study. By asking the participants about the actual frequencies of medication since the last visit, the medication adherence rate will be calculated as follows: $100 \times$ frequency of taking medication since last visit/assigned frequency of medication since last visit. As a secondary endpoint, adverse events will be analysed using the safety analysis set, which includes participants who received an assigned treatment at least once. Continuous and categorical variables will be presented as the mean±SD or median (25–75th quartiles) and as frequencies with percentages, respectively.

The primary endpoint, the percentage change in fasting apoB-48 level from baseline to 16 weeks, will be compared between the two groups using the unpaired t-test. The secondary endpoints will be analysed using the paired t-test or Wilcoxon’s signed-rank test for within-group comparisons, the unpaired t-test or Mann-Whitney U test for comparisons between two groups and an analysis of covariance for comparisons between two groups as appropriate. The relationship between fasting apoB-48 and clinical variables at 16 weeks will be assessed using Pearson’s or Spearman’s correlation analysis. The baseline characteristics of the participants in the two groups will be compared by using the $\chi^2$ test or Fisher’s exact test for categorical variables and t-test or Mann-Whitney U test for continuous variables. All p values will be two sided with $p<0.05$ taken to indicate statistical significance.

All statistical analyses will be performed by the study statistician (MS) at the data centre (Nexis, Fukuoka, Japan) using SPSS V.26 (IBM).

**Availability of data and materials**

The datasets generated and/or analysed during the study will be available from the corresponding author on reasonable request after the final report of the trial has been published.

**Patient and public involvement**

Patients and/or the public were not involved in planning the design, performance, reporting or dissemination of this research.

**ETHICS AND DISSEMINATION**

This study has been registered with the Japan Registry of Clinical Trials (jRCT) (No. jRCTs071200011), which is the
clinical research database of the Ministry of Health, Labour and Welfare of Japan and is approved as a WHO Primary Registry. The study protocol is version 1.31 created on 16 January 2020, and was approved by the Certified Review Board of the University of the Ryukyus for Clinical Research Ethics (No. CRBR200001) on 26 February 2020. Written informed consent will be obtained from all participants. Results from the study will be disseminated through publications and conference presentations to participants, healthcare professionals and the public.

**DISCUSSION**

Although therapeutic interventions for hypertriglyceridaemia have been proposed to reduce the residual risk of ASCVD in patients with dyslipidaemia treated with statins, there is no rationale for choosing these agents. There is no doubt that both pemafibrate and PUFAs are important hypertriglyceridaemia drugs. Furthermore, both drugs may be used in combination to reduce the residual risk of ASCVD with statin treatment, as they not only decrease TG levels but also increase HDL-C levels. Therefore, this prospective, multicentre, open-label, randomised, parallel group trial was designed to compare the effects of pemafibrate and omega-3 on the fasting apoB-48 level.

With regard to the appropriateness of the primary endpoint of this study, previous studies, including those conducted in Japan, have shown that hypertriglyceridaemia is associated with ASCVD, especially CAD, even after adjusting for HDL-C levels, suggesting that therapeutic interventions for hypertriglyceridaemia may reduce the residual risk of ASCVD. However, the use of fasting or non-fasting parameters to assess hypertriglyceridaemia as a risk factor for ASCVD is debatable. Based on several studies and a meta-analysis, the assessment of elevated TG level for predicting ASCVD is currently considered more useful in the non-fasting state, and diagnostic criteria for non-fasting hypertriglyceridaemia have been set in Europe.

ApoB-48 is an apolipoprotein synthesised in the intestine that affects TRLs, which are thought to be the main cause of postprandial hypertriglyceridaemia and are independent risk factors for ASCVD. ApoB-48 may be beneficial for postprandial hypertriglyceridaemia because of the relationship between fasting apoB-48 level and the incremental AUC for postprandial TG level. Further, it could be a useful marker of ASCVD risk, as fasting apoB-48 is correlated with both the prevalence of CAD and carotid IMT. Therefore, we feel that it is appropriate to use apoB-48 as the primary study endpoint to compare the effects of pemafibrate and omega-3 on postprandial hypertriglyceridaemia.

With regard to whether the doses of pemafibrate and Omega-3 are appropriate, in comparing the lowering effects of pemafibrate and omega-3 on fasting apoB-48, we considered that findings based on comparisons between maximum doses that can be applied clinically as therapeutic agents for hypertriglyceridaemia are of great clinical significance. In addition, in previous studies conducted in Japanese patients with hypertriglyceridaemia receiving statin treatment, the approximate percentage changes in TG levels before and after treatment with pemafibrate at 0.4 mg/day, omega-3 at 2 g/day and omega-3 at 4 g/day were reported to be −50%, −10% and −20%, respectively. Considering these findings, it was assumed that omega-3 at a dose of 2 g/day may be obviously inferior to pemafibrate at 0.4 mg/day with regard to the percentage change in fasting apoB-48 level. Therefore, pemafibrate at 0.4 mg/day and omega-3 at 4 g/day, which are the maximum clinical doses, will be used to compare the lowering effects of these two drugs on fasting apoB-48 level in this study.

The strength of this study is that it will be the first trial to compare the lowering effects of pemafibrate and omega-3 on fasting apoB-48, a surrogate marker reflecting postprandial hypertriglyceridaemia, which could be a residual risk factor for ASCVD with statin treatment. We believe that this study will provide important insight into whether pemafibrate or omega-3 should be used to treat hypertriglyceridaemia to reduce the residual risk of ASCVD in patients receiving LDL-C-lowering treatment. In addition, we also expect that this study will provide new insights into the differences in favourable antiatherosclerotic effects of pemafibrate and omega-3 on lipid and glucose metabolism, such as remnant lipoprotein cholesterol, small dense LDL-C, GP-HPLC lipoprotein subfractions, fasting plasma glucose and HOMA-IR.

This study has several potential limitations. First, the effects of pemafibrate and omega-3 on atherosclerotic cardiovascular outcomes represented by MACE cannot be evaluated. Second, as this is an open-label trial, there are concerns about potential bias and its impact on the results.

Finally, we believe that this study will provide useful evidence on the choice of therapeutic agents for hypertriglyceridaemia in patients with dyslipidaemia treated with statins and will contribute to reducing the occurrence of ASCVD.
COMPETING INTERESTS YT, MO and MS have no potential competing interests to disclose. IS received an honorarium for a lecture from GlaxoSmithKline and research funding from Kowa. SJ has received honoraria for lectures from Bayer Yakuhin, Daiichi Sankyo, Kowa, Mitsubishi Tanabe Pharma, MSD, Novartis Pharma, Otsuka Pharmaceutical and Takada Pharmaceutical. SU has received honoraria for lectures from Daiichi Sankyo, Kowa and Taiko Pharmaceutical and grants from Bayer Yakuhin, Bristol-Myers Squibb and Kowa.

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