PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Pemafibrate for treating MASLD complicated by hypertriglyceridemia: A multi-center, open-label, randomized controlled trial study protocol

Authors

Iwaki, Michihiro; Kobayashi, Takashi; Nogami, Asako; Ogawa, Yuji; Imajo, Kento; Sakai, Eiji; Nakada, Yoshinobu; Koyama, Satoshi; Kurihashi, Takeo; Oza, Noriko; Kohira, Toshikazu; Okada, Michiaki; Yamaguchi, Yuki; Iwane, Shinji; Kageyama, Fujito; Sasada, Yuzo; Matsushita, Masahiro; Tadauchi, Akimitsu; Murohisa, Gou; Nagasawa, Masamichi; Sato, Shuichi; Maeda, Kazuhisa; Furuta, Koichiro; Shigefuku, Ryuta; Seko, Yuya; Tobita, Hiroshi; Kawata, Kazuhito; Kawanaka, Miwa; Sugihara, Takaaki; Tamaki, Nobuharu; Iwasa, Motoo; Kawaguchi, Takumi; Itoh, Yoshito; Kawaguchi, Atsushi; Takahashi, Hirokazu; Nakajima, Atsushi; Yoneda, Masato

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Razmi, Hamidreza**
Affiliation	**Ahvaz Jundishapur University of Medical Sciences**
Date	**01-Jun-2024**
COI	**I have no competing interests**

Thanks for the opportunity to review this manuscript.

This study assessed the effectiveness of a Pemafibrate on NAFLD, a prevalent health issue in societies. Here are my comments and suggestions:

1. The abstract gives a clear overview of the study design and rationale. However, including additional details, such as the type of study, participant information like age, and secondary and exploratory endpoints, would enhance the abstract further.

2. How did you evaluate compliance with the study protocol and medication regimen? What measures were taken to ensure that participants adhered to the study requirements?

3. Please provide a reference for the statement "doses approved for essential dyslipidemia were used." This will help readers understand the rationale behind the dosage regimen used in the study.

4. Please provide a reference for the specific entry criteria used to define hypertriglyceridemia and elevated ALT.

5. How was the assessment of food intake and physical activity conducted? Were validated tools or questionnaires used to collect this data? Factors such as BMI, physical activity, and food intake can influence the development and progression of non-alcoholic fatty liver disease. Were these factors considered as potential confounding variables in the study analysis?

6. What was the maximum BMI of the patients included in the study? Were normal weight, overweight, and obese individuals considered together in the analysis?

Reviewer	**2**
Name	**Xiong, Zhenyu**
Affiliation	**Sun Yat-sen University First Affiliated Hospital**
Date	**14-Aug-2024**
COI	**none.**

Comment 1: Endpoint Timing and Justification

The manuscript specifies that the primary endpoint is a change in ALT levels after 24 weeks of pemafibrate administration, despite the total treatment duration being 48 weeks. Given that one of the study's aims is to assess the long-term efficacy and safety of pemafibrate, the choice of a 24-week time point as the primary endpoint warrants clarification. Please provide a detailed rationale for selecting this specific time point and discuss how it aligns with the long-term goals of the study.

Comment 2: Standardization of Blood Tests in Multi-Center Trials

Given the multi-center nature of the trial, it is crucial to standardize blood testing procedures to ensure consistency across different sites. Different hospitals may use varying equipment for assessing biomarkers. Please detail the approach that will be used to standardize these tests, including any standardized methods or quality control measures implemented.

Comment 3: Pemafibrate Dosage Information

The manuscript currently presents the dosage information for high and low doses of pemafibrate in the supplemental materials. For better accessibility and clarity, this information should be included in the main manuscript. Please revise the manuscript to include detailed descriptions of the dosage regimens used in the study.

Comment 4: Screening Test Timing Clarification

The protocol mentions that “blood collection, electrocardiography, and imaging tests within three months of obtaining consent may be substituted for screening tests.” It is unclear whether this implies that tests conducted within three months prior to obtaining consent can also be used for screening purposes. Please clarify this point to ensure that the protocol’s requirements for screening tests are clearly understood.

Comment 5: Language and Formatting Issues

Several language and formatting errors need addressing:

Repeated sentences are found on lines 345-346, page 15.

There are formatting issues in the supplemental material on page 4, specifically with the table format. Please correct these errors to improve the clarity and presentation of the manuscript.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. Hamidreza Razmi, Ahvaz Jundishapur University of Medical Sciences
Comments to the Author:
Thanks for the opportunity to review this manuscript.
This study assessed the effectiveness of a Pemafibrate on NAFLD, a prevalent health issue in societies. Here are my comments and suggestions:
1. The abstract gives a clear overview of the study design and rationale. However, including additional details, such as the type of study, participant information like age, and secondary and exploratory endpoints, would enhance the abstract further. 1.
Our response:
Thank you for your valuable comments.
As you noted, the abstract revised to include all the necessary information accordingly (Page 3).

2. How did you evaluate compliance with the study protocol and medication regimen? What measures were taken to ensure that participants adhered to the study requirements?
Our response:
Thank you for your valuable comments.
Regarding adherence to the medication regimen, it is described in the Medication instructions on Page 18, Lines 459-471. When delivering the investigational drug, the physician in charge instructed the patient to take the drug, and the patient was asked to bring the remaining medication.
The compliance with the study protocol was monitored as described in Page 17. As you pointed out, the description was insufficient, and we have added a corresponding note to Pages 17-18, Lines 447-451.

3. Please provide a reference for the statement "doses approved for essential dyslipidemia were used." This will help readers understand the rationale behind the dosage regimen used in the study.
Our response:
Thank you for your insightful suggestion.
The dose of pemafibrate was set in compliance with the Drug Information for Drug Administration in Japan, referring to the Phase III clinical trial in patients with dyslipidemia (Ishibashi S et al. J Clin Lipidol 2018;12:173–84).
Because of the risk of hepatotoxicity with fenofibrate, the Japanese guidelines state that for patients with abnormal liver function test results or a history of hepatotoxicity, the daily dose of fenofibrate should be

started at 53.3 mg. The dosage of fenofibrate was set based on this information.
We have added this text to Page 7, Lines 200-204.

4. Please provide a reference for the specific entry criteria used to define hypertriglyceridemia and elevated ALT.

Our response:
The inclusion criteria for hypertriglyceridemia encompassed TG levels of 150–500 mg/dL, based on a phase III trial evaluating the efficacy of Palmodia in patients with hypertriglyceridemia. (Ishibashi S et al. J Clin Lipidol 2018;12:173–84).
The lower limit of elevated ALT levels, as an inclusion criterion, was set at 43 for males and 24 for females, in accordance with the Japanese Committee for Clinical Laboratory Standards (JCCLS) (Ichihara K et al. Ann Clin Biochem 2016, 53(Pt 3):347-356). Furthermore, given that hepatotoxicity associated with fenofibrate has been reported in the Drug Information for Fenofibrate in Japan, it is recommended that administration should be discontinued if AST or ALT consistently exceeds 2.5 times the upper limit of normal or 100 units. In reference to this, the upper limit of ALT in the participation criteria was set at 100.
These statements are listed in Page 9, Lines 260-267.

5. How was the assessment of food intake and physical activity conducted? Were validated tools or questionnaires used to collect this data? Factors such as BMI, physical activity, and food intake can influence the development and progression of non-alcoholic fatty liver disease. Were these factors considered as potential confounding variables in the study analysis?

Our response:
Thank you for your pointing this out. Food intake and physical activity have not been evaluated. We have included this in the limitations section (Page 20, Lines 542-545). This study is already underway, so it is difficult to obtain this information. However, as it is a very important point, we plan to include it in the items to be investigated when designing future clinical trials.

6. What was the maximum BMI of the patients included in the study? Were normal weight, overweight, and obese individuals considered together in the analysis?

Our response:
Thank you for your comment. This trial is still in progress and we have not yet recovered all the data.
We are very interested in this point and will publish the data as soon as we have analyzed them.

Reviewer: 2
Dr. Zhenyu Xiong, Sun Yat-sen University First Affiliated Hospital
Comments to the Author:
Comment 1: Endpoint Timing and Justification
The manuscript specifies that the primary endpoint is a change in ALT levels after 24 weeks of pemafibrate administration, despite the total treatment duration being 48 weeks. Given that one of the study's aims is to assess the long-term efficacy and safety of pemafibrate, the choice of a 24-week time point as the primary endpoint warrants clarification. Please provide a detailed rationale for selecting this specific time point and discuss how it aligns with the long-term goals of the study.

Our response:
Thank you for your very valuable remarks.
Serum ALT is a sensitive indicator of hepatocyte injury and inflammation. The ALT-lowering effect of pemafibrate has been observed as early as 4 weeks (Arai H et al. J Atheroscler Thromb 2018, 25(6):521-538), with stable reductions reported from 24 to 52 weeks (Araki E et al. Diabetes Obes Metab 2019, 21(7):1737-1744). To assess the sustained, long-term impact on ALT, the study was conducted in both the United States and Japan. A 24-week period was deemed sufficient to evaluate the stable, long-term effect on ALT levels. On the other hand, we determined that a longer follow-up period of up to 48 weeks was necessary to evaluate liver fibrosis via fibrosis markers and elastography. We have included these statements on Page 6, Lines 181-184.

Comment 2: Standardization of Blood Tests in Multi-Center Trials

Given the multi-center nature of the trial, it is crucial to standardize blood testing procedures to ensure consistency across different sites. Different hospitals may use varying equipment for assessing biomarkers. Please detail the approach that will be used to standardize these tests, including any standardized methods or quality control measures implemented.

Our response: Thank you for your pertinent comment. It is extremely important to standardize blood testing procedures among different facilities as you have indicated. Since not all facilities use the same analytical methods, measurement principles, calibrators, and reagents, test results may vary from one facility to another. This is a clinical study conducted in the usual practice, and the basic endpoints, with the exception of liver fibrosis markers, which are measured centrally, are measured according to the methods prescribed by each facility. Since there is no unified standardized approach in this study, we have included this in the limitations section (Page 20, Lines 542-545).

Although we cannot change the protocol of this study because it is already in progress, this is a crucial point, and we will try to standardize the testing protocol in the planning phase of future studies.

Comment 3: Pemafibrate Dosage Information

The manuscript currently presents the dosage information for high and low doses of pemafibrate in the supplemental materials. For better accessibility and clarity, this information should be included in the main manuscript. Please revise the manuscript to include detailed descriptions of the dosage regimens used in the study.

Our response:

Thank you for your valuable comment.

On Pages 7-8, Lines 214-227, we have detailed the dosage information for the high and low doses of pemafibrate.

Comment 4: Screening Test Timing Clarification

The protocol mentions that "blood collection, electrocardiography, and imaging tests within three months of obtaining consent may be substituted for screening tests." It is unclear whether this implies that tests conducted within three months prior to obtaining consent can also be used for screening purposes. Please clarify this point to ensure that the protocol's requirements for screening tests are clearly understood.

Our response:

Thank you for your invaluable comment. We apologize for the unclear wording. We have revised the text to express that tests performed within 3 months prior to obtaining consent can also be used for screening tests (Page 13, Line 313-314).

Comment 5: Language and Formatting Issues

Several language and formatting errors need addressing:

- Repeated sentences are found on lines 345-346, page 15.
- There are formatting issues in the supplemental material on page 4, specifically with the table format. Please correct these errors to improve the clarity and presentation of the manuscript.

Our response:

Thank you for your valuable comment.

The text on Page 16, line 388, was incorrectly written and has been revised from "Violation of concomitant use of prohibited drugs" to "Violation of concomitant use of prohibited therapies." The text in 9.1. Target population for analysis in Supplementary document 1 has been revised accordingly.

The tables in 7.1.7.1. Schedule and 1.6.1.1. Schedule of the Study in Supplementary documents 1 and 2 have also been partially revised.

Finally, we would like to express our sincere gratitude to the editors and reviewers for their positive and constructive criticism. Your valuable and insightful comments and suggestions have greatly improved the manuscript. Also, since the name was changed from NAFLD to MASLD in 2023, we have changed the notation 'NAFLD' to 'MASLD' in this revision. This has also been noted in the Introduction and Discussion sections. We look forward to receiving your response. If necessary, we will be happy to answer any questions you

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Razmi, Hamidreza**
Affiliation	**Ahvaz Jundishapur University of Medical Sciences**
Date	**22-Oct-2024**
COI	

The authors have adequately addressed the comments, and I recommend its acceptance for publication.