PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference **W-3984PCT**	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2007/061099	31.05.2007	31.05.2006

International Patent Classification (IPC) or both national classification and IPC

Applicant

MOCHIDA PHARMACEUTICAL CO., LTD.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ the translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims		YES
	Claims	1-8	NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations:

This written opinion is based on documents 1-5 below cited in the ISR. Documents 4-5 were published after the priority date of the present application (31 May 2006), but are referenced to certify the contents disclosed in documents 1-3.

Document 1: "AHA Hatsu Sokuho JELIS Kekka Happyo," Medical Tribune, 17 November 2005, Tokubetsu Kikaku Dai 3 Bu, pages 75-76 (Doitsu Naiyo no Website Kiji: URL, http://www.medical-tribune.jp/congress/jelis/jelis.html)

Document 2: YOKOYAMA, M. *et al.*, "Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS)," American Heart Journal, (2003), Vol. 146, No. 4, pages 613-620

Document 3: Yuichi ISHIKAWA, "JELIS no Jisshi Keikaku to Kitai sareru Kekka," [online], JELIS Medical Asahi (Medical Asahi December 1996 Bassui), [29 March 2007 Access], Internet, URL, http://www.mochida.co.jp/dis/jelis/jlnwepm2.htm

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1

Document 4: Yasushi SAITO, "Fukusu no Risk Inshi ga Juseki shita Shorei no Kandomyaku Event Ichiji Yobo ni Okeru EPA Seizai no Yuyosei," [online], AHA2006 Sokuho JELIS Sub Kaiseki Kekka Happyo, [29 March 2007 Access], Internet, URL, http://www.jelis.jp/mt/aha2006/01_01.html, http://www.mtrib.com/mt/aha2006/01_01.html

Document 5: MOCHIDA PHARMACEUTICAL CO., LTD. News Release, "'Epadel' ga Kandomyaku Shikkan no Hassho to Saihatsu o Yokusei Daikibo Shiken 'JELIS' no Aratana Kaiseki Kekka ga Kohyo sare mashita," 15 November 2006 Happyo, URL, http://www.mochida.co.jp/news/2006/pdf/1115.pdf

The invention as set forth in claims 1-8 is described in documents 1-3 and is not novel and does not involve an inventive step.

Documents 1-3 describes the trial design and backgrounds of subject patients of a large-scale clinical trial (JELIS trial) publicly conducted over 1996 through 2005 in order to verify the hypothesis that long-term concomitant dosing with high-purity eicosapentaenoic acid ethyl ester (EPA-E) and HMG-Co-A reductase inhibitor (pravastatin or simvastatin) prevents the onset and recurrence of cardiovascular events in patients with hypercholesterolemia more effectively than dosing with HMG-Co-A reductase inhibitor alone. Document 1 provides the results following the completion of the JELIS trial, and document 2 describes the conditions of implementing the trial during 2003.

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Documents 1-3 also indicate that the EPA-E preparation used in the abovementioned JELIS trial falls within the scope stipulated by claims 4-5 of the present application with respect to EPA-E content, dose, dosing period, etc. Documents 2-3 indicates that an additional 25% inhibition of the onset of cardiovascular events that dosing with HMG-Co-A reductase inhibitor alone cannot prevent is anticipated from the concomitant dosing of EPA-E and HMG-Co-A reductase inhibitor in the JELIS trial.

In addition, given that documents 1-3 indicates that the total number of patients suffering from hypercholesterolemia who are subjects in the JELIS trial will exceed 10,000, it is estimated that these subjects will also include as a matter of course patients suffering from complications that present multiple risk factors, such as obesity, hypertension, diabetes, hypertriglyceridemia, and low HDL-C levels.

In fact, documents 4-5, which were published after the priority date of the present application, describe the sub-analysis results of the JELIS trial, and indicate that in the group dosed with EPA-E, in the primary preventive cases suffering from hypercholesterolemia as well as other risk factors (obesity, hypertension, diabetes, hypertriglyceridemia, and low HDL-C levels), the onset of cardiovascular events was inhibited in all risk combination groups compared to the control group, and that specifically, the onset of cardiovascular events was inhibited notably among patients suffering from a combination of hypertriglyceridemia and low HDL-C levels.

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Documents 1-3 do not provide specific trial results such as those provided in documents 4-5; however, the subject patient group in the JELIS trial clearly included those with the abovementioned complications of multiple risk factors, and documents 1-3 are found to indicate that the effect of concomitant dosing with EPA-E and HMG-Co-A reductase inhibitor including the effect of inhibiting the onset of cardiovascular events was anticipated in those patients as well.

Hence, the invention as in claims 1-8 of the present application is the inventions as set forth in documents 1-3, and was publicly implemented prior to the priority date of the present application.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date (day/*month*/*year*)	Filing date (day/*month*/*year*)	Priority date (valid claim) (*day*/month/*year*)
WO 2007/007686 A1 [EX]	18.01.2007	07.07.2006	08.07.2005

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/*year*)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Upon reference to the description in paragraph [0025] of the description in the present application, the disclosure of claim 6, "characterized by concomitant use with a 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitor," is understood to mean both the embodiment wherein the composition that is the invention of the present application is simply administered to a patient; and the embodiment wherein the composition in the present application, which has eicosapentaenoic acid ethyl ester (EPA-E) as an active ingredient, also contains 3- hydroxy-3-methylglutaryl coenzyme-A reductase inhibitor (HMG-CoA RI) as a compounding ingredient. However, these two forms specify different components in the composition that is the invention of the present application; thus, the disclosure of claim 6 does not convey a single unified technical concept, and thus, is unclear.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:

A61K31/232(2006.01)i, A61K45/00(2006.01)i,
A61P3/04(2006.01)i, A61P3/06(2006.01)i,
A61P3/10(2006.01)i, A61P9/00(2006.01)i,
A61P9/10(2006.01)i, A61P9/14(2006.01)i,
A61P43/00(2006.01)i, A61K31/22(2006.01)n,
A61K31/351(2006.01)n