Appeal Decision

Appeal No.2019-14815

Appellant	ASTRAZENECA PLC
Patent Attorney	ONO, Shinjiro
Patent Attorney	YAMAMOTO, Osamu
Patent Attorney	MIYAMAE, Toru
Patent Attorney	NAKANISHI, Motoharu
Patent Attorney	TERACHI, Takumi

The case of appeal against the examiner's decision of refusal for Japanese Patent Application No. 2017-539261 entitled "METHOD OF TREATING OR PREVENTION OF ATHEROTHROMBOTIC EVENTS IN PATIENTS WITH HISTORY OF MYOCARDIAL INFARCTION" [International Publication WO 2016/120729 on August 4, 2016; National Publication of International Patent Application No. 2018-502894 on February 1, 2018] has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reasons

1. History of the procedures

The present application was filed as an international patent application dated on January 27, 2016 (claim of priority under the Paris Convention: January 27, 2015; February 5, 2015; February 18, 2015; March 13, 2015; March 14, 2015; May 1, 2015; May 4, 2015; August 28, 2015; all of which are under United States of America (US)), and the history of the procedures is summarized as follows:

December 8, 2017	Submission of Written Amendments and Written Petition
August 28, 2018	Notification of Reasons for Refusal

February 4, 2019	Submission of Written Amendments and Written Opinion
June 27, 2019	Decision of Refusal
November 5, 2019	Submission of Written Correction of Mistranslation and Notice of Appeal
December 9, 2019	Reconsideration Report
August 19, 2020	Submission of Written Petition
January 26, 2021	Notification of Reasons for Refusal
July 27, 2021	Submission of Written Amendment and Written Opinion

2. The Present Invention

The inventions according to Claims 1 to 15 in the scope of claims of the present application are specified by the matters recited in Claims 1 to 15 in the scope of claims amended by the Written Amendments submitted on July 27, 2021. The invention according to Claim 1 (hereinafter referred to as "the Present Invention") is as follows:

"[Claim 1]
A pharmaceutical composition comprising:

ticagrelor for use in preventing one or more major adverse cardiovascular events by delaying the first occurrence of the major adverse cardiovascular events in a patient in recognized need of preventing major adverse cardiovascular events, as compared to a dosing regimen where the patient receives a daily maintenance dose of 75 mg to 150 mg aspirin only, wherein

the use includes a step of administering to the patient twice daily the pharmaceutical composition containing 60 mg ticagrelor,

the one or more major adverse cardiovascular events are selected from cardiovascular death, myocardial infarction, and stroke,

the patient has a history of myocardial infarction at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor, and

the patient is also administered the daily maintenance dose of aspirin of 75 mg to 150 mg."

3. Summary of the Notification of Reasons by the Body

Among Reason No. 3 in the Notification of Reasons for Refusal dated January 26, 2021, which is the reason for refusal by the Body, the reason for refusal of Claim 1 regarding Article 29(2) of the Patent Act is as follows:

The invention according to Claim 1 of the present application should not be granted a patent under the provisions of Article 29(2) of the Patent Act, because the invention could have been easily invented by a person skilled in the art before the priority date of the present application based on the invention described in Cited Document 2 and the matters described in Cited Document 3.

<List of Cited Documents>

Cited Document 2: ANONYMOUS, PEGASUS-TIMI 54 STUDY OF BRILINTA TM-ASTRAZENECA, [ONLINE], January 14, 2015, [retrieved on 2016-05-24], Retrieved from the Internet, URL, https://www.astrazeneca.com/media-centre/press-releases/2015/pegasus-timi-54-study-brilinta-reduction-cardiovascular-thrombotic-events-14012015.html

Cited Document 3: American Heart Journal, 2014, Vol.167, No.4, p.437-444.e5

Cited Document 6: "Future Clinical Trials: Scientific Evaluation of Drugs - Principles and Methods", October 1, 1999, first edition, p.1 to 13, p.86 to 87 (document of common technical knowledge)

*Note by the Body: Cited Document 2 is a press release published on the Global website of AstraZeneca; however, only the above title and date of search of Cited Document 2 are incorrect, and the correct details are as follows:

Note that the underlines are added by the Body. "(R)" refers to the circled R (the same applies hereinafter).

"Cited Document 2: PEGASUS-TIMI 54 study of BRILINTA(R) meets primary endpoint in both 60 mg and 90 mg doses, [ONLINE], January 14, 2015 [retrieved on 2017/12/04], Retrieved from the Internet, URL, https://www.astrazeneca.com/media-centre/press-releases/2015/pegasus-timi-54-study-brilinta-reduction-cardiovascular-thrombotic-events-14012015.html"

4. Matters Described in Cited Documents 2 and 3

(1) Cited Document 2

Since the original text is written in a foreign language, quotations are made in

Japanese translation by the Body as necessary. The underlines are added by the Body (the same applies hereinafter).

(Quotation 2a)
"PEGASUS-TIMI 54 study of BRILINTA(R) meets primary endpoint in both 60mg and 90mg doses"
(Title of the document)

(Quotation 2b)
"Both BRILINTA 60 mg and 90 mg demonstrate statistically significant reduction in major cardiovascular thrombotic events in patients with a history of heart attack.

AstraZeneca today announced that the PEGASUS-TIMI 54 study, a large scale outcomes trial involving over 21,000 patients, successfully met its primary efficacy endpoint. The study assessed BRILINTA(R) (ticagrelor) tablets at either 60mg twice daily or 90mg twice daily plus low-dose aspirin for the secondary prevention of atherothrombotic events in patients who had experienced a heart attack one to three years prior to study start. The primary efficacy endpoint was a composite of cardiovascular (CV) death, myocardial infarction (MI) or stroke.

Preliminary analysis did not reveal any unexpected safety issues. Full evaluation of the data is ongoing.
...
The PEGASUS-TIMI 54 study investigated two different doses of ticagrelor on a background of low dose aspirin versus placebo plus low dose aspirin, in patients aged 50 and older with a history of heart attack and one additional CV risk factor. The study was designed to better understand the management of patients more than 12 months after their heart attack, who remain at high risk for major thrombotic events."
(Title of the item "Both BRILINTA...heart attack" under the title of the document and paragraphs 1, 2, and 4 of the text)

(Quotation 2c)
"PEGASUS-TIMI 54 (PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group) is one of AstraZeneca’s largest ever outcomes trials with more than 21,000 patients from over 1,100 sites in 31 countries in Europe,

the Americas, Africa and Australia/Asia. It was conducted in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group from Brigham and Women's Hospital (Boston, MA, USA)."
(Lines 1-5 of the text of "About PEGASUS-TIMI 54")

(Quotation 2d)
"[1]Bonaca MP, Bhatt DL, Braunwald E, et al. ... Am Heart J.2014; 167: 437-44." (Text of "NOTES FOR EDITORS")

(2) Cited Document 3

(Quotation 3a)
"Design and rationale for the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial"
(Title of the document)

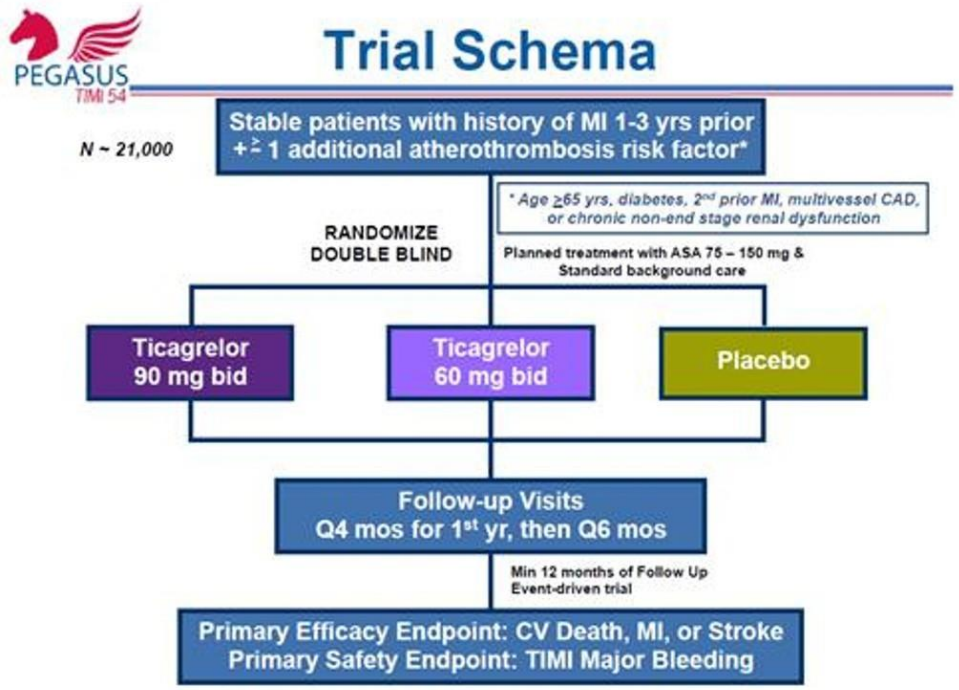
(Quotation 3b)
"Study Design: PEGASUS-TIMI 54 is a randomized, double-blind, placebo-controlled, multinational clinical trial designed to evaluate the efficacy and safety of ticagrelor in addition to aspirin (75-150 mg) for the prevention of major adverse cardiovascular events in patients with a history of myocardial infarction and risk factors. Patients with a history of spontaneous myocardial infarction within 1 to 3 years are randomized in a 1:1:1 fashion to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or matching placebo, all with low dose ASA, until the end of the study. The primary endpoint is a composite of cardiovascular death, myocardial infarction, or stroke. Recruitment began in October 2010 and completed in April 2013 with a sample size of over 21,000 patients. The trial is planned to continue until the latest of either 1,360 adjudicated primary end points are accrued or the last patient randomized has been followed for at least 12 months.
Conclusion: PEGASUS-TIMI 54 is investigating whether the addition of intensive antiplatelet therapy with ticagrelor to low-dose aspirin reduces major adverse cardiovascular events in high-risk patients with a history of myocardial infarction."
("Study Design" and "Conclusions" in the Abstract on p.437)

*Note by the Body: "ASA" is an abbreviation for aspirin.

(Quotation 3c)
"Table 1. Inclusion/Exclusion Criteria
Inclusion Criteria
At least 50 years old
Spontaneous MI within 1-3 years prior
plus at least one of the following risk factors
...
Taking ASA: 75 - 150 mg daily dose"
("Table 1. Inclusion/Exclusion Criteria" on p.439)

*Note by the Body: "MI" is an abbreviation for myocardial infarction.

(Quotation 3d)
"



Study Schema for PEGASUS-TIMI 54. *CAD*, Coronary artery disease; *MI*, myocardial infarction.

"
("Figure" on p.438)

(Partial translation of Quotation 3d)
"Primary Efficacy Endpoint: CV Death, MI or Stroke

Primary Safety Endpoint: TIMI Major Bleeding"
(Bottommost square box of "Figure")
"Study schema for PEGASUS-TIMI 54. CAD, Coronary artery disease; MI, myocardial infarction"
(Bottommost line of "Figure")

5. Cited Invention

The Cited Document 2 is the document entitled "PEGASUS-TIMI 54 study of BRILINTA(R) meets primary endpoint in both 60mg and 90mg doses" (Quotation 2a), and describes that BRILINTA (R) is a ticagrelor tablet (Summary 2b), and it is interpreted that 60 mg and 90 mg doses indicate the doses of active ingredient (ticagrelor) in BRILINTA (R).

The Cited Document 2 discloses that in the "PEGASUS-TIMI 54 study" conducted by AstraZeneca and targeting over 21,000 patients, a composite of cardiovascular death, myocardial infarction or stroke was set as the primary efficacy endpoint, and that the study investigated two different doses of ticagrelor, including 60 mg (twice daily) or 90 mg (twice daily), on the background of low dose aspirin, versus placebo plus low-dose aspirin, in patients aged 50 and older with a history of heart attack one to three years prior to the study start and one additional CV (vascular) risk factor (Quotation 2b, 2c).

Further, the Cited Document 2 also discloses that the "PEGASUS-TIMI 54 study" met its primary efficacy endpoint and the preliminary analysis did not reveal any unexpected safety issues (Quotation 2b).

Therefore, the following invention (hereinafter referred to as "the Cited Invention") is considered to be described in Cited Document 2.

"A ticagrelor tablet for use in the "PEGASUS-TIMI 54 study", whose result met its primary efficacy endpoint, which is a composite of cardiovascular death, myocardial infarction, or stroke, and whose preliminary analysis did not reveal any unexpected safety issues, wherein

in the study, the patients who have experienced a heart attack one to three years prior to the study start are administered twice daily 60mg ticagrelor plus low-dose aspirin."

6. Comparison and Judgment

(1) Comparison

Comparison is made between the Present Invention and the Cited Invention.

In the Cited Invention, "the patients who have experienced a heart attack one to three years prior to the study start" are targeted patients for the PEGASUS-TIMI 54 study whose "primary efficacy endpoint" is "a composite of cardiovascular death, myocardial infarction, or stroke", and therefore, it is interpreted that the patients are those in recognized need of preventing "cardiovascular death, myocardial infarction, or stroke" and corresponds to "a patient in recognized need of preventing major adverse cardiovascular events" in the Present Invention.

Further, since a "tablet" usually comprises an active ingredient and a pharmaceutically acceptable carrier, the "ticagrelor tablet" in the Cited Invention by which patients are "administered twice daily 60mg ticagrelor" corresponds to the "pharmaceutical composition" "comprising 60 mg ticagrelor" and administered in the "step of administering to the patient twice daily" in the Present Invention.

Furthermore, "experienced a heart attack one to three years prior to the study start" in the Cited Invention and "has a history of myocardial infarction at least 12 months prior to" in the Present Invention are common in "having a history of heart disease at least 12 months before."

Moreover, " are administered twice daily 60mg ticagrelor plus low-dose aspirin" in the Cited Invention is recognized to mean that aspirin is administered daily, and the "low-dose" is recognized to mean a "maintenance dose", and therefore, "administered" "plus low-dose aspirin" in the Cited Invention corresponds to "the daily maintenance dose of aspirin" is also "administered" in the Present Invention.

Therefore, the corresponding features and differences between the Present Invention and the Cited Invention are as follows.

<Corresponding features>

"A pharmaceutical composition comprising:

ticagrelor to be administered to a patient in recognized need of preventing major adverse cardiovascular events, wherein

the pharmaceutical composition comprising 60 mg ticagrelor is administered by a step of administering twice daily,

the patient has a history of heart disease at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising the 60 mg ticagrelor, and the patient is also administered a daily maintenance dose of aspirin."

<Difference 1>

In the Present Invention, the daily maintenance dose of aspirin is "75 mg to 150 mg", whereas in the Cited Invention, the daily maintenance dose of aspirin is "low-dose" and no specific numerical value is specified.

<Difference 2>

In the Present Invention, the history of heart disease is "myocardial infarction", whereas in the Cited Invention, the history of heart disease is "heart attack".

<Difference 3>

In the Present Invention, the use of the pharmaceutical composition is "use in preventing one or more major adverse cardiovascular events by delaying the first occurrence of the major adverse cardiovascular event in a patient in recognized need of preventing major adverse cardiovascular events, as compared to a dosing regimen where the patient receives a daily maintenance dose of 75 mg to 150 mg aspirin only", and "the one or more major adverse cardiovascular events are selected from cardiovascular death, myocardial infarction, and stroke", whereas in the Cited Invention, the use of the pharmaceutical composition is "use in the PEGASUS-TIMI 54 study", whose result of the study "met its primary efficacy endpoint, which is a composite of cardiovascular death, myocardial infarction, or stroke, and whose preliminary analysis did not reveal any unexpected safety issues."

(2) Judgment

A. Regarding Differences 1 and 2

(a) In the Cited Document 2, the document referred as "[1]Bonaca MP, Bhatt DL, Braunwald E, et al. ..., Am Heart J.2014; 167: 437-44." (Quotation 2b, 2d), which is cited as a reference for the "PEGASUS-TIMI 54 study", is the Cited Document 3.

Here, the Cited Document 3 describes that the PEGASUS-TIMI 54 was a clinical trial designed such that patients with a history of spontaneous myocardial infarction within 1 to 3 years were targeted, and efficacy and safety were evaluated in the case where 90 mg ticagrelor or 60 mg ticagrelor is administrated twice daily in addition to daily administration of 75-150 mg aspirin (Quotation 3b to 3d), that the primary efficacy endpoint of the trial was a composite of CV (cardiovascular) death, myocardial infarction, or stroke, and that the primary safety endpoint of the trial was TIMI (Thrombosis in Myocardial Infarction) major bleeding (Quotation 3b to 3d).

Further, since the PEGASUS-TIMI 54 study in the Cited Document 2 is interpreted to mean the same study as the PEGASUS-TIMI 54 trial in the Cited Document 3, the "heart attack" in the Cited Invention means the "myocardial infarction" described in the Cited Document 3, and the "low-dose aspirin" in the Cited Invention

means aspirin (75-150 mg), i.e., "75 mg to 150 mg aspirin", described in the Cited Document 3.

Therefore, Differences 1 and 2 are not substantial differences.

(b) Discussion will be made assuming that Differences 1 and 2 are substantial differences.

a. Regarding Difference 1

It is a matter of course for a person skilled in the art to determine a specific dose of the "low-dose aspirin" when administering ticagrelor tablets with the dose and method specified in the Cited Invention, and thus, adopting the "75 mg to 150 mg aspirin" administered in the PEGASUS-TIMI 54 trial in the Cited Document 3 (Quotation 3b to 3d), which is interpreted to mean the same study as the PEGASUS-TIMI 54 study in the Cited Document 2, is merely a matter easily conceived by a person skilled in the art.

b. Regarding Difference 2

It was a common technical knowledge at the time of the priority date of the present application, that is chemic heart disease such as myocardial infarction was a typical example of a disease that causes a heart attack (If necessary, Reference A; IMAMURA, Hiroshi, "The 6th Public Lecture, Emergency Response and Treatment Policies for Heart Attack," 2009, Physiotherapy Research, Nagano, No.38, p.16-18).

Further, since in the PEGASUS-TIMI 54 study in the Cited Document 2, which is interpreted to mean the same study as the PEGASUS-TIMI 54 trial in the Cited Document 3, patients with a history of spontaneous myocardial infarction within 1 to 3 years are targeted (Quotation 3b to 3d), a person skilled in the art can easily specify the "heart attack" in the Cited Invention as the "myocardial infraction" described in the Cited Document 3 based on the above-mentioned common technical knowledge (Reference A) and the description of the Cited Document 3.

c. As discussed above, it cannot be said that special creativity is required to adopt the matters relating to the Differences 1 and 2 into the Cited Invention.

B. Regarding Difference 3

(a) The "endpoint" is a setting of what the impact of an intervention content will be seen in advance in a clinical trial whose purpose is to compare interventional treatments, etc. (the Cited Document 6: p.86, lines 1-5 of the text).

The "PEGASUS-TIMI 54 study" in the Cited Invention investigated two different doses of ticagrelor on a background of low dose aspirin versus placebo plus low-dose aspirin (Quotation 2b). "[W]hose result met its primary efficacy endpoint, which is a

composite of cardiovascular death, myocardial infarction or stroke" in this study is interpreted to mean that patients "administrated twice daily 60 mg ticagrelor plus low-dose aspirin" have a reduced incidence of "cardiovascular death, myocardial infarction, or stroke" as compared to patients administrated "placebo plus low-dose aspirin", that is "only low dose aspirin".

Further, "cardiovascular death, myocardial infarction, or stroke" in the Cited Invention corresponds to "major adverse cardiovascular events" in the Present Invention.

(b) As discussed in the above (a), it can be recognized that the "low-dose aspirin" in the Cited Invention is "75- 150 mg aspirin" when referring to the Cited Document 3.

(c) Therefore, a person skilled in the art who had seen the descriptions of the Cited Documents 2 and 3 would have obviously understood that, since the administration of ticagrelor tablets in the Cited Invention had reduced the incidence of "cardiovascular death, myocardial infarction, or stroke" as compared to a case of administrating "75-150 mg aspirin" only, the first occurrence of the major adverse cardiovascular events could be delayed, and that the prevention of such events could be achieved.

Therefore, it could have been conceived by a person skilled in the art with ease to adopt the matters relating to the Difference 3 into the Cited Invention.

C. Regarding Effects of the Present Invention

(a) In the Specification of the present application, the results of the PEGASUS-TIMI 54 study are described in detail as the example, referring Figs. 1 to 26 and Tables 1 to 24.

Specifically, the results of the clinical trial ([0111] to [0118], etc.) are described in which patients with a history of spontaneous myocardial infarction 1 to 3 years prior to enrollment and one of the additional high risk features are administrated with aspirin at a dose of 75 to 150 mg daily and are further orally administered, in randomized 1:1:1 fashion, with 90 mg ticagrelor twice daily (hereafter referred to as "90 mg group"), 60 mg ticagrelor twice daily (hereafter referred to as "60 mg group"), or placebo (hereafter referred to as "placebo group"), and the main effects derived from the above study results are described in the following (i) to (iii).

(i) The 90 mg and 60 mg groups achieved a similar magnitude of efficacy in the intention-to-treat analysis ("Table 8. Efficacy Endpoints" in [0133], [0190], etc.).

(ii) The Hazard Ratio (HR) for Fatal Bleeding in the third year when the 60 mg group is compared to the placebo group was 1.00. ("Items for Fatal Bleeding" in the right column in "Table 14. Safety and Tolerability Endpoints" in [0148], etc.).

(iii) The rates of bleeding and dyspnea were numerically lower in the 60 mg group as

compared to the 90 mg group and a lower treatment discontinuation rate and better tolerability were obtained in the 60 mg group ("Table 14. Safety and Tolerability Endpoints" in [0148], [0190], etc.).

(b) On the other hand, in the Cited Document 2, it is stated that "[f]ull evaluation of the data is ongoing." (Quotation 2b), the detained results of the PEGASUS-TIMI 54 study are not described, and as the dose of ticagrelor with an administration twice daily, it is not described that 60 mg dose was superior to 90 mg dose in terms of treatment discontinuation rate and tolerability.

However, the Cited Document 2 describes that both 60 mg and 90 mg doses achieved the primary efficacy endpoint (composite of cardiovascular death, myocardial infarction, or stroke) in the PEGASUS-TIMI 54 study, and since it can be said that, from this description, a person skilled in the art could understand that both doses are effective for treatment, and the effect of the Present Invention described in the above (i) is not particularly remarkable enough to be considered to have an inventive step.

Further, since the "preliminary analysis did not reveal any unexpected safety issues" in the Cited Invention, the effect of the Present Invention in the above (ii), that the hazard ratio for fatal bleeding in the 60 mg group as compared to the placebo group is 1.00 in the third year, is also not particularly remarkable, and can be predicted by a person skilled in the art.

Furthermore, because a dose of a smaller amount of active ingredients is generally better in tolerance (tolerability) with fewer side effects, the effect of the Present Invention in the above (iii), that the rates of bleeding and dyspnea as side effects are numerically lower in the 60 mg group than in the 90 mg group, and the 60 mg group had lower treatment discontinuation rates and better tolerability, is merely an effect that could have been predicted by a person skilled in the art.

Therefore, even considering the results of the PEGASUS-TIMI 54 study (Figs. 1 to 26, Tables 1 to 24, etc.) described in the example in the Specification of the present application, the effect of the Present Invention cannot be said to be an exceptionally remarkable effect that cannot be predicted by a person skilled in the art based on the invention described in the Cited Document 2, matters described in the Cited Documents 2 and 3, and common technical knowledge (the Cited Document 6, the Reference A).

(3) Summary

According to the above discussion, based on the invention described in the Cited Document 2, the matters described in the Cited Documents 2 and 3, and the common technical knowledge (the Cited Document 6, the Reference A), the Present Invention

could have been easily made by a person skilled in the art.

7. Regarding Appellant's allegation

The appellant alleges that, based on the results of the PEGASUS-TIMI 54 study described in the Specification of the present application, not only it was confirmed that long-term dual antiplatelet therapy with ticagrelor and aspirin is an effective treatment, but also it was found that a dose of 60 mg ticagrelor twice daily in the long-term dual antiplatelet therapy and a dose of 90 mg ticagrelor twice daily in the long-term dual antiplatelet therapy have equivalent efficacy (Table 8); the dose of 60 mg ticagrelor twice daily shows a better risk profile than the dose of 90 mg ticagrelor twice daily (Table 14); the Present Invention has a significantly remarkable effect that cannot be expected by a person skilled in the art even taking the cited documents into consideration; and in this regard, the Present Invention has the inventive step (Page 4 of the Written Opinion submitted on July 27, 2021).

However, as described in the above (a) and (b) in (2) of 6, the configuration of the Present Invention could have been easily conceived by a person skilled in the art. The effect of the Present Invention which shows the efficacy equivalent to that in the case of using 90 mg ticagrelor and a better risk profile than the case of using 90 mg ticagrelor cannot be said to be particularly remarkable effect, and can be predicted by a person skilled in the art, as also described in the above c in (2) of 6.

Therefore, the above allegation of the appellant cannot be adopted.

8. Closing

As stated above, the invention according to Claim 1 of the present application should not be granted a patent under the provisions of Article 29(2) of the Patent Act. Therefore, the present application shall be rejected even without examining the inventions claimed in the other claims.

Thus, the appeal decision shall be made as described in the conclusion.

October 26, 2021

Chief administrative judge: MAEDA, Kayoko
Administrative judge: FUJIWARA, Hiroko
Administrative judge: FUCHINO, Ruka