Trial decision

Invalidation No. 2016-800080

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The case of trial regarding the invalidation of Japanese Patent No. 3874419, entitled "Medicament for Prevention of and Treatment for Arteriosclerosis and Hypertension" between the parties above has resulted in the following trial decision:

Conclusion

The correction of the scope of claims of Japanese Patent No. 3874419 shall be approved as the corrected scope of claims attached to the written correction request, and

the correction of Claims 6 to 25 shall be approved.

The trial of the case was groundless.

The costs in connection with the trial shall be borne by the demandant.

Reason

1. History of the procedures

Japanese Patent No. 3874419 of the case is a patent application filed on January 29, 2004 as an international filing date (priority claim: January 31, 2003 and February 7, 2003), and the establishment of patent right was registered on November 2, 2006.

Against this, a trial for invalidation of the case was demanded by the demandant, and the written demand for trial submitted on July 5, 2016 is to request invalidation of the Patent of the case according to Claims 6 to 25. In addition, a written reply and a written correction request were submitted by the demandee on September 20, 2016, and a response letter to Inquiry was submitted on November 10, 2016.

Further, the demandant and the demandee respectively submitted oral proceedings statement briefs on January 17, 2017, and the demandant and the demandee respectively made statements in 1st oral proceeding held on January 31, 2017, as described in 1st oral proceeding record.

In the above oral proceedings statement brief, the demandant additionally alleges that there are Reason for invalidation 3 of lack of inventive step based on Evidence A No. 6 or the like and Reason for invalidation 4 due to deficiency of requirements for support . However, since the allegation of Reasons for invalidation 3 is to add reasons for invalidation based on a newly main cited document and the allegation of Reasons for invalidation 4 is to add reasons for invalidation in accordance with the provisions of a new article, it should be said that both allegations are amendments for changing gist of statement of the demand, and a decision on acceptance or non-acceptance of amendment that the amendment cannot be recognized in accordance with the provisions of Article 131-2(1) of the Patent Act was made at the above oral proceeding.

2. Request for correction

According to the description of written correction request on September 20, 2016, the object of request for correction and content of correction of the case are as follows.

2-1. Object of request for correction

To request to correct the scope of claims of Japanese Patent No. 3874419 to Claims 6 to 25 after the correction, as the corrected scope of claims attached to written correction request of the case.

2-2. Content of Correction

(1) Correction A

The correction A is to correct "a medicament comprises a compound (A) and a compound (B) as active ingredients" of Claim 6 of the scope of claims, to "a medicament consists of a compound (A) and a compound (B) as active ingredients."

(2) Correction B

The correction B is to correct "a medicament comprises a compound (A) and a compound (B) as active ingredients" of Claim 7 of the scope of claims, to "a medicament consists of a compound (A) and a compound (B) as active ingredients, and has an effect of inhibiting arteriosclerosis by inhibiting remodeling of the vessels."

2-3. Judgment of suitability of correction

(1) Regarding the Correction A

It can be said that the Correction A is to limit "comprises a compound (A) and a compound (B) as active ingredients" of Claim 6 to "consists of a compound (A) and a compound (B) as active ingredients," and the Correction A corresponds to restriction of the scope of claims.

Further, it is described in the Description attached to the application of the Patent (hereinafter referred to as "the Description of the case") that "The present medicament is manufactured by previously known methods by using pharmacologically acceptable and suitable additive agents (carriers) such as excipients, lubricants, binders, disintegrants, emulsifiers, stabilizers, flavours, diluents, and the like, if necessary, in addition to the compound (A) and the compound (B), which are the active ingredients." (lines 7 to 9 on page 12 of the Patent). Further it is described in Examples of the Description of the case that olmesartan medoxomil corresponding to the compound (A) and azelnidipine corresponding to the compound (B) are only used. According to these descriptions, it can be said that "consists of a compound (A) and a compound (B) as

active ingredients" is described in the Description of the case. Thus, the Correction A is within the scope of the matters described in the Description of the case, and does not substantially expand or change the scope of claims.

(2) Regarding the Correction B

It can be said that the Correction B is to limit "comprises a compound (A) and a compound (B) as active ingredients" of Claim 7 to "consists of a compound (A) and a compound (B) as active ingredients," similar to the Correction A, and to limit "a medicament" of Claim 7 to "a medicament has effect of inhibiting arteriosclerosis by inhibiting remodeling of the vessels," and thus the Correction B corresponds to restriction of the scope of claims.

Further, as described above, it can be said that "consists of a compound (A) and a compound (B) as active ingredients" is described in the Description of the case. In addition, it is described in the Description of the case that "The present invention is to provide medicaments that effectively inhibit remodeling of vessels and prevent progression of arteriosclerosis as well as restenosis of vessels following PCI." (lines 33, 34 on page 4 of the Patent), "As concretely shown in the Test Examples of the present specification, the medicament of the present invention consisting of the compound (A) and the compound (B) works synergistically and inhibits neointima formation of blood vessels and proliferation of vascular smooth muscle cells and, as a result, inhibits vascular remodeling. Based on the actions described above, the medicaments of the present invention can be used for the prophylaxis of restenosis following percutaneous coronary intervention in addition to the prophylaxis and/or treatment of arteriosclerosis." (lines 22 to 26 on page 11 of the Patent), the title of Example 1 is "Inhibitory Effects Against Arteriosclerosis," and "When 0.1 mg/kg/day of azelnidipine and 0.5 mg/kg/day of olmesartan were administered at the same time, ... it was clearly demonstrated in vivo that co-administration of azelnidipine and olmesartan improves vascular remodeling." (lines 7 to 12 on page 14 of the Patent). According to these descriptions, it can be said that the "a medicament consists of a compound (A) and a compound (B) as active ingredients, and has an effect of inhibiting arteriosclerosis by inhibiting remodeling of the vessels." Thus, the Correction B is within the scope of the matters described in the Description of the case, and does not substantially expand or change the scope of claims.

Further, since each of Claims 8 to 25 is directly or indirectly dependent on Claim 6 or 7 to be requested for correction, Claims 6 to 25 before the correction

correspond to a group of claims. Thus, correction is requested for each group of claims.

(3) Closing

Therefore, request for correction of the case is intended for the matters listed in Article 134-2(1)(i) of the Patent Act, and it falls under the provisions of Article 126(5) and (6) of the Patent Act which is applied mutatis mutandis pursuant to the provisions of Article 134-2(3) and (9), and Claims 6 to 25 after the correction shall be approved.

3. Corrected invention of the case

As the correction is approved, the inventions according to Claims 1 to 25 of the scope of claims of Japanese Patent No. 3874419 of the case are specified by the matters described in Claims 1 to 25 of the corrected scope of claims of the case, and Claims 6 to 25 (hereinafter referred to as "the Corrected invention of the case 6" to "the Corrected invention of the case 25" in order) are as follows.

"[Claim 6]

A medicament for the prevention and/or treatment of hypertension or a disease derived from hypertension, wherein the medicament consists of the compound (A) and the compound (B) according to Claim 1 as active ingredients.

[Claim 7]

A medicament for the prevention and/or treatment of hypertension or a disease derived from hypertension, wherein the medicament consists of the compound (A) and the compound (B) according to Claim 1 as active ingredients, and the medicament has effect of inhibiting arteriosclerosis by inhibiting remodeling of the vessels.

[Claim 8]

The medicament according to Claim 6, wherein the disease derived from hypertension is heart disease.

[Claim 9]

The medicament according to Claim 6, wherein the disease derived from hypertension is angina pectoris.

[Claim 10]

The medicament according to Claim 6, wherein the disease derived from hypertension is myocardial infarction.

[Claim 11]

The medicament according to Claim 6, wherein the disease derived from hypertension is arrhythmia.

[Claim 12]

The medicament according to Claim 6, wherein the disease derived from hypertension is sudden death.

[Claim 13]

The medicament according to Claim 6, wherein the disease derived from hypertension is heart failure.

[Claim 14]

The medicament according to Claim 6, wherein the disease derived from hypertension is cardiac hypertrophy.

[Claim 15]

The medicament according to Claim 6, wherein the disease derived from hypertension is a renal disease.

[Claim 16]

The medicament according to Claim 6, wherein the disease derived from hypertension is diabetic nephropathy.

[Claim 17]

The medicament according to Claim 6, wherein the disease derived from hypertension is glomerulonephritis.

[Claim 18]

The medicament according to Claim 6, wherein the disease derived from hypertension is nephrosclerosis.

[Claim 19]

The medicament according to Claim 6, wherein the disease derived from hypertension is a cerebrovascular disease.

[Claim 20]

The medicament according to Claim 6, wherein the disease derived from hypertension is cerebral infarction.

[Claim 21]

The medicament according to Claim 6, wherein the disease derived from hypertension is cerebral hemorrhage.

[Claim 22]

The medicament according to any of Claims 1 to 21, wherein the compound (A) is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-carboxylate.

[Claim 23]

The medicament according to any of Claims 1 to 22, wherein the medicament is

a pharmaceutical composition comprising the compound (A) and the compound (B) as active ingredients.

[Claim 24]

The medicament according to Claim 23, wherein the medicament is a physically single formulation.

[Claim 25]

The medicament according to any of Claims 1 to 22, wherein the medicament is for administering the compound (A) and the compound (B) at the same time or separately at certain intervals."

4. The party's allegation, and Evidence

4-1. Reasons for invalidation alleged by the demandant, and Evidence

The demandant demands the decision, "The patent for the invention according to Claims 6 to 25 of the scope of claims of Japanese Patent No. 3874419 shall be invalidated. The costs in connection with the trial shall be borne by the demandee.", and alleges the following Reasons for invalidation 1 and 2, and submitted Evidence A No. 1 to 21 as a means of proof.

(Reasons for invalidation 1)

The Corrected inventions of the case 6 to 25 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 8 and well-known arts if necessary, taking into account Evidence A No. 9 and No. 14 to No. 17, and the Corrected inventions of the case 6 to 25 lack an inventive step.

Thus, the Patent for the Corrected inventions of the case 6 to 25 violates the provisions of Article 29(2) of the Patent Act, and should be invalidated under the provisions of Article 123(1)(ii).

(Reasons for invalidation 2)

The Corrected inventions of the case 6 to 25 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 10 and well-known arts if necessary, taking into account Evidence A No. 9 and No. 15 to No. 17, and the Corrected inventions of the case 6 to 25 lack an inventive step.

Thus, the Patent for the Corrected inventions of the case 6 to 25 violates the provisions of Article 29(2) of the Patent Act, and should be invalidated under the provisions of Article 123(1)(ii).

(Evidence)
Evidence A No. 1: Ethical Drug package Insert, Japanese Pharmacopoeia, olmesartan medoxomil tablet and olmesartan medoxomil orally disintegrating tablet;
URL
http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/430574_2149044F1024_3_19
Evidence A No. 2: Ethical Drug package Insert, Japanese Pharmacopoeia, azelnidipine tablet;
URL
https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/671423_2149043F1038_1_05
Evidence A No. 3: Guidelines for hypertension therapy, 2000, pages 5 and 31 to 37
Evidence A No. 4: Arakawa et al., "Clinical evaluation of angiotensin II-receptor antagonist BIBR277 (telmisartan) with combination therapy of calcium antagonist or thiazide diuretic to patients having mild or moderate essential hypertension", Jpn Pharmacol Ther vol. 30 supplement 2002
Evidence A No. 5: National Publication of International Patent Application No. H6-503834
Evidence A No. 6: U.S. patent publication No. 2001/0049384 and partial translation thereof
Evidence A No. 7: International Publication No. WO00/27396 and partial translation thereof
Evidence A No. 8: Japanese Patent No. 3057471
Evidence A No. 9: Oishi et al., "Outlook on new drug regarding antihypertensive agent in 2002", Medicine and Drug Journal, Vol. 38, S-1, 2002/p.127-p.130
Evidence A No. 10: Smith, "Strategies to Meet Lower Blood Pressure Goals with a New Standard in Angiotensin II Receptor Blockade", AJH 2002; 15:108S-114S and partial translation thereof
Evidence A No. 11: Daiichi Sankyo Co., Ltd., Information on Rezaltas combination tablets LD and Rezaltas combination tablets HD
URL http://www.pmda.go.jp/drugs/2010/P201000016/index.html Outline of non-clinical study (1) Pharmacological Test, CS-866AZ 2.6.2 Outline of Pharmacological Test
(The above items of Evidence are attached to Request for trial.)
Evidence A No. 3-1: Guidelines for hypertension therapy, 2000, pages 83 to 101, colophon

Evidence A No. 6-1: Partial translation of Evidence A No. 6
Evidence A No. 12: Collection on utilization of animal model for new drug development, issued on June 10, 1985, pages 141 to 158, colophon
Evidence A No. 13: Study on human life and culture, Int J Hum Cult Stud., 2015, No. 25, pp. 191-193
Evidence A No. 14: Stephanie F Gardner et al., The Annals of Pharmacotherapy, "Olmesartan Medoxomil: The Seventh Angiotensin Receptor Antagonist", 2003 January, Volume 37, p. 99-105
Evidence A No. 14-1: Partial translation of Evidence A No. 14
Evidence A No. 14-2: Search results of documents in Annals of Pharmacotherapy, retrieved on January 1, 2003.
Evidence A No. 15: Sata et al., Jpn Pharmacol Ther, "Anti-atherogenic action of high lipophilic long-acting calcium antagonist azelnidipine on cholesterol loading rabbits", 2002, vol. 30, no. 9, pp. 721-728
Evidence A No. 16: Sata et al., Jpn Pharmacol Ther, "Pharmacological properties of long-acting calcium antagonist azelnidipine having vascular affinity (Part 1)", 2002, vol. 30, no. 9, pp. 703-709
Evidence A No. 17: Sata et al., Jpn Pharmacol Ther, "Pharmacological properties of long-acting calcium antagonist azelnidipine having vascular affinity (Part 2)", 2002, vol. 30, no. 9, pp. 711-720
Evidence A No. 18: Okunishi, Progress in Medicine, "Action of antihypertensive agent on risk factor of ischemic heart disease, 3. Anti-atherogenic action of antihypertensive agent", 1997. 9, Vol. 17, No. 9, pp. 2398-2403
Evidence A No. 19: Shimamoto, The Journal of Therapy, "Antihypertensive therapy for patient having complication, hypertension with hyperlipidemia", (2000, 4), Vol. 82, No. 4, pp. 59-65
Evidence A No. 20: Japanese Unexamined Patent Application Publication No. H5-78328
Evidence A No. 21: Japanese Unexamined Patent Application Publication No. S63-253082
(The above items of Evidence are attached to the oral proceedings statement brief.)

4-2. The demandee’s allegation, and Evidence

The demandee demands the decision, "The request for correction shall be approved, the trial of the case was groundless, and the costs in connection with the trial shall be borne by the demandee.", and challenges the allegation by the demandant that

the Patent is groundless, and submitted Evidence B No. 1 to 21 as a means of proof.

(Evidence)
Evidence B No. 1: Comment booklet of "Guidelines for hypertension therapy" for the public, hypertension, The Japanese Society of Hypertension, Board for creating Guidelines for hypertension therapy (2014)
Evidence B No. 2: Japanese Journal of Clinical Medicine, vol. 72 extra number, 6 (2014) pages 51 to 55
Evidence B No. 3: Inaba et al., American Journal of Hypertension, Vol. 22, No. 2, pp. 145-150 (2009) and partial translation thereof
Evidence B No. 4: EPO minutes of oral proceedings of objection dated on April 1, 2011 regarding EP Patent No. 1 096 932 the inventors of which are the same as those of Evidence A No. 6, and partial translation thereof
Evidence B No. 5: Statement from Mr. Mizuno
Evidence B No. 6: Statement from Mr. Shinagawa
Evidence B No. 7: Farumashia, Vol. 44, No. 6, pp. 537-541 (2008)
Evidence B No. 8: Progress in Medicine, Vol. 23, No. 4, pp. 1145-1150 (2003)
Evidence B No. 9: Guidelines for hypertension therapy, cover, table of contents, Chapter 5 (pages 37 to 45) (2009)
Evidence B No. 10: Guidelines for hypertension therapy, cover, table of contents, Chapter 5 (pages 45 to 57) (2014)
Evidence B No. 11: Wada et al., Hypertens Res Vo. 19, No. 4, 247-254 (1996) and partial translation thereof
Evidence B No. 12: Chikuma HAMADA, Statistics for presentation on conference or article, cover, pages 30 to 37 and 94 to 99, colophon (1999)
(The above items of Evidence are attached to a written reply dated September 20, 2016. Evidence B No. 5 is replaced by that attached to a response letter dated November 10, 2016.)
Evidence B No. 13: Inaba et al., American Journal of Hypertension, Vo. 22, No. 2, 145-150, attached with Supplemental Figure 1 (2009)
(The above items of Evidence are attached to an oral proceedings statement brief dated 2016.)
Evidence B No. 14: Calcium antagonists (second edition), SENTAN IGAKU-SHA Ltd., cover, pages 414 to 432, colophon (1999)
Evidence B No. 15: Journal of Human Hypertension, 16 (Suppl 2), S7-S12 (2002) and partial translation thereof

Evidence B No. 16: Vascular Health and Risk Management, 7, pp. 383-390 (2011) and partial translation thereof
Evidence B No. 17: Drug Design, Development and Therapy, 7, pp. 175-183 (2013) and partial translation thereof
Evidence B No. 18: [digest version] Guideline for non-invasive evaluation of vascular function, pp. 113-145 (2013)
Evidence B No. 19: Atherosclerosis, 66, pp. 63-76 (1987) and partial translation thereof
Evidence B No. 20: Atherosclerosis, 65, pp. 199-205 (1987) and partial translation thereof
Evidence B No. 21: Lifestyle and Genetic disease, Medical Review Co., Ltd., cover, pages 91 to 102, colophon (2002)
(The above items of Evidence are attached to a written statement dated January 31, 2017.)

5. Described matters in Evidences
5-1. Described matters in respective items of Evidence A
The descriptions of Evidence A No. 1 to A No. 21 are as follows.

Evidence A No. 1
(Indication 1A)
Pages 1 and 5
Regarding olmesartan medoxomil of compound (A) of the patent invention, it is described that "Olmesartan medoxomil is an active ingredient of Olmetec tablets.", "10 mg of Olmetec tablets (Approval number: 21600AMZ00031) and 20 mg of Olmetec tablets (Approval number: 21600AMZ00032) have been sold from Daiichi Sankyo Co., Ltd. since May, 2004.", and "Olmetec tablets have efficacy on hypertension."

Evidence A No. 2
(Indication 2A)
Pages 1 and 4
Regarding azelnidipine of compound (B) of the patent invention, it is described that "Azelnidipine is an active ingredient of Calblock tablets.", "8 mg of Calblock tablets (Approval number: 21500AMZ00030) and 16 mg of Calblock tablets (Approval number: 21500AMZ00031) have been sold from Daiichi Sankyo Co., Ltd. since May, 2003.", and "Calblock tablets have efficacy on hypertension."

Evidence A No. 3
(Indication 3A)
Last paragraph on page 5

"This guideline is for normal present therapy in Japan; needless to say, the guideline should be corrected or updated on the basis of evaluation from Society of Hypertension, other related conferences or medical associations, and the result of major clinical trials to be published. We hope that the guideline helps clinicians engaging in hypertensive therapy."

(Indication 3B)
Line 10 in the right column on page 32 to line 17 in the left column on page 33
"a) Decision of first line

Recently, calcium antagonists, ACE inhibitors, AII receptor antagonists, diuretics, β blockers (including αβ blockers) and α blockers [5, 9] have been mainly used; however, there is no result of significant effect on prognosis of each antihypertensive agent in RCT. Thus, it has been thought that efficacy of therapy using the antihypertensive agent does not result from a property peculiar to antihypertensive agents, but from antihypertensive action itself. However, since it has been recently shown that doxazosin of α blockers has weak effect for improving prognosis on cardiovascular disease in ALLHAT trail (Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial) in the US, doxazosin has possibility of not being suitable as first line [118, 119]. Taking the following factors into consideration, antihypertensive agents should be selected to be suitable for individual patients.
*Cardiovascular risk factors - smoking, hyperlipidemia, obesity, impaired glucose tolerance, family history of cardiovascular disease, and the like
*Target organ damage, cardiovascular disease
*Adverse effects of antihypertensive agent, effect on QOL

A case of being desirably put to positive use and a case of contraindication are shown in Table 5-2.
Table 5-2 (omitted)

b) Switching and addition of antihypertensive agent
*To avoid adverse effects with unpredicted and excessive antihypertensive action, administration of antihypertensive agent is started with single agent and low dose.
*long-acting antihypertensive agent with single daily dose is used.
*Slowly exhibiting antihypertensive action is desirable and the purpose is to reach target

blood pressure after 2 or 3 months.
*In a case of failure to reach target pressure of less than 140/90 mmHg (for non-elderly adults, less than 130/85 mmHg, if possible), the amount is increased, if tolerated; however the amount is not more than twice the normal amount. Even so, in a case of failure to reach the target pressure, low dose antihypertensive agent of other class is additively combined.

Combinations often used in RCT or practical clinic are as follows.
(1) Calcium antagonist and ACE inhibitor (or AII receptor antagonist)
(2) Dihydropyridinec calcium antagonist and β blocker
(3) ACE inhibitor (or AII receptor antagonist) and diuretic
(4) β blocker and α blocker
(5) Diuretic and β blocker
*In a case where there is little effect with initially used antihypertensive agent or there is poor tolerability, the agent is switched to an antihypertensive agent of another class."
(Note: the above (1) to (5) are symbols in which each number of 1 to 5 is indicated in ○.)

(Indication 3C)
Line 12 in the left column to line 11 in the right column on page 34
"(a) Calcium antagonist

Calcium antagonists have been developed as antianginal agents, and it has been shown that the calcium antagonists have antihypertensive action by dilating not only coronary artery but also peripheral arteriole.

Dihydropyridine calcium antagonist and benzothiazepin calcium antagonist are used as antihypertensive agents; the benzothiazepin calcium antagonist is limited to only diltiazem. 14 kinds (18 forms) of calcium antagonist have been available commercially, and there is a significant difference in duration of action between nifedipine initially developed and amlodipine or nifedipine recently developed.

Nifedipine has fast-acting and potent antihypertensive action; on the other hand, this agent has a defect of activating the sympathetic nervous system or the renin-angiotensin system with hypertensive action such that the heart rate or workload of the heart is increased. Especially, when administering short-acting nifedipine capsules, potent hypertensive action is shown; on the other hand, the action is weakened after 2 or 3 hours, blood pressure is susceptible to be unstable, and there is possibility to impair ischemic heart disease [120)]. Thus, long-acting nifedipine should be used. Amlodipine has slow antihypertensive action, long-acting action and antihypertensive action, and

thus this agent does not have an effect on heart rate. (omitted)"

(Indication 3D)
Line 9 to last line in the left column on page 35
"(c) AII receptor antagonist

It has been known that angiotensin II receptors have type I to IV receptors. Action of most of known angiotensin II is through type I receptor, and AII receptor antagonist is an agent having antihypertensive action by selectively inhibiting action of angiotensin II through this type I receptor. In Japan, losartan and candesartan have been commercially available in recent years.

Antihypertensive action is thought to dilate peripheral vessels, inhibit the secretion of aldosterone, and inhibit release of noradrenaline from sympathetic nerve terminals. Since enzymes producing angiotensin II from angiotensin I, such as chymase and cathepsin G, are present in the cardiovascular system, along with ACE, angiotensin II is produced even when inhibiting ACE. Thus, it is thought that AII receptor antagonists inhibit renin-angiotensin system more specifically than ACE inhibitors. When using AII receptor antagonist, renin production is increased, so that angiotensin II acts on AII receptor antagonistic action of angiotensin II through the receptor and is thought to inhibit elevation of blood pressure or progression of organ damage.

AII receptor antagonists have slow and reliable antihypertensive action, and exhibit excellent additive or synergetic effect in combination with a diuretic or calcium antagonist.

AII receptor antagonists have less adverse effects [125)], such as dizziness and palpitation similar to that of placebo, and thus this agent is useful for continuous treatment [126), 127)].

Precautions are in conformity with ACE inhibitors."

(Indication 3E)
Line 16 to last line in the right column on page 37
"Conclusion
1) When using antihypertensive agents, you should get the correct facts of properties and adverse effects of each agent to read the package insert, and you should select and use the most suitable agent depending on the clinical condition of each patient.
2) Agents recommended as first line are calcium antagonists, ACE inhibitors, AII receptor antagonists, a few diuretics, β blockers, and α blockers. In a case where one agent among these agents is administered to exhibit slow antihypertensive action but the

action is insufficient, you should use the agent in combination with another agent having additive or synergetic effect, or switch to another agent.
3) In a case of failure to reach target blood pressure, you should seek advice from an expert in hypertension."

Evidence A No. 4
(Indication 4A)
Page S-121 to line 29 in the left column on page S-122

"Clinical evaluation of angiotensin II-receptor antagonist BIBR277 (telmisartan) with combination therapy of calcium antagonist or thiazide diuretic to patients having mild or moderate essential hypertension -late phase II combination therapy trial-
(omitted)
Introduction

The purpose of hypertensive therapy is to inhibit progression of principal organ damage with antihypertensive action, so as to prevent the onset of cardiovascular disease. According to "Guidelines for hypertension therapy in 2000"[1)], target blood pressure is less than 130/85 mmHg in a case of younger-aged people, middle-aged people, or diabetic patients, and in a case of elderly people, 140 to 160 mmHg or less regarding systolic blood pressure and less than 90 mmHg regarding diastolic blood pressure. As a rule for using antihypertensive agents, (1) single daily dosing antihypertensive agent is generally selected, (2) firstly, the dosage amount of antihypertensive agent is low dose, (3) therapy in combination with antihypertensive agent to inhibit adverse effects and enhance antihypertensive action is performed, (4) if there is less antihypertensive action when initially administering antihypertensive agent or if not tolerated, the antihypertensive agent is switched to another antihypertensive agent different in mechanism of action, (5) if it is associated with other disease, interaction between agents to be administered should be confirmed. In Japan, various excellent antihypertensive agents can be used, target blood pressure has become lower, and it has seen that some single agents have difficulty reaching the target blood pressure.

As described above, to reach the target blood pressure, when a single agent does not have sufficient antihypertensive action, taking long-term hypertensive therapy in general and the clinical condition or complication of patients into consideration, it is recommended that a plurality of antihypertensive agents that are different in mechanism of action be used in combination with low dose. As a combination of antihypertensive agents, antihypertensive agents are generally different in mechanism of action, and according to the above guideline, in a case of angiotensin II type 1 (AT1) receptor

antagonist, calcium antagonist or diuretic is used in combination. In Japan, the calcium antagonists are most commonly used, and frequency of the formulation in Japan is higher than that in other foreign countries, and therapy with antihypertensive agent and calcium antagonist in combination is used for about 60% of patients with hypertension. Thus, regarding hypertensive therapy in Japan, the combination of antihypertensive agent and calcium antagonist is thought to be the most commonly used combination for treating patients having mild or moderate essential hypertension."
(Note: the above (1) to (5) are symbols in which each number of 1 to 5 is indicated in ○.)

(Indication 4B)
Second line from the bottom in the right column on page S-122 to line 4 in the left column on page S-124

"As described above, in the clinical trial, to patients having mild or moderate essential hypertension who did not obtain sufficient antihypertensive action even when calcium antagonist or thiazide diuretic was administered, single daily dosing of 20 mg to 80 mg of the agent was added, antihypertensive action and safety of therapy in combination with the agent was evaluated, and clinically recommended dose was examined.
('Table 1' is omitted)"

(Indication 4C)
Lines 30 to 34 in the right column on S-136

"As described above, in the clinical trial, to patients who did not obtain sufficient antihypertensive action when calcium antagonist or thiazide diuretic was administered with single agent, dosing of 20 mg to 80 mg of the agent was added, and it was shown that good antihypertensive action was exhibited."

Evidence A No. 5
(Indication 5A)
Claims 43 to 49
"43. A method of treating hypertension which comprises a step of administering stepwise or in physical combination of a calcium channel blocker and an angiotensin II-receptor antagonist selected from compounds of the formulae (I) to (IX), as described in claim 1.
44. The method of treating hypertension which comprises a step of administering

stepwise or in physical combination a calcium channel blocker and an angiotensin II-receptor antagonist selected from compounds of the formula (I).
45. The method of claim 44, wherein the angiotensin II-receptor antagonist is (E)-3-[2-n-butyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoic acid or a pharmaceutically acceptable salt thereof.
46. The method of claim 45, wherein the angiotensin II-receptor antagonist is (E)-3-[2-n-butyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoic acid methanesulfonate.
47. The method of claim 46, wherein the calcium channel blocker is nifedipine, diltiazem, or verapimil.
48. The method of claim 44, wherein the angiotensin II-receptor antagonist is (E)-3-[2-n-butyl-1-{(4-carboxynaphth-1-yl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid or a pharmaceutically acceptable salt thereof.
49. The method of claim 48, wherein the calcium channel blocker is nifedipine, diltiazem, or verapimil."

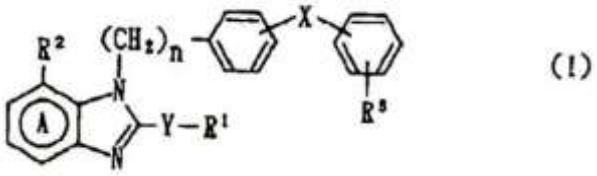
Evidence A No. 6
(Indication 6A)
Abstract

"This invention relates to a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (omitted), and stroke, comprising a step of administering a therapeutically effective amount of (i) AT1-antagonist of valsartan or pharmaceutically acceptable salt thereof and (ii) a calcium channel blocker or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, to a mammal in need thereof, and to a corresponding pharmaceutical combination composition."

Evidence A No. 7
(Indication 7A)
Abstract

"Combinations comprising diethyl (E)-4-[2-(tert-butoxycarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (lacidipine) and 4'-[[2-n-propyl-4-methyl-6-(1-methylbenziimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid (telmisartan), pharmaceutical compositions containing the combinations, and their use in the treatment of cardiovascular disorders including hypertension."

Evidence A No. 8
(Indication 8A)
Claims 1, 19, and 22
"[Claim 1] A preventive or therapeutic agent for angiotensin II-mediated diseases comprising a compound having antagonistic action of angiotensin II and represented by general formula (I) or a salt thereof, in combination with a compound having diuretic action or a compound having calcium antagonistic action.
[Chem. 1]



(I)

(wherein, R^1 represents hydrogen or a hydrocarbon group which may be substituted, R^2 represent a carboxyl group which may be esterified, R^3 represents a group which may form a negative ion or may be changed into the negative ion, X represents that a phenylene group and a phenyl group are bound directly or through a space having 2 atom chains, n represents 1 or 2, a ring A represents a benzene ring which may have a substituent other than a group represented by R^2, Y represents a bond, -O-, -S(O)m- (wherein m represents 0, 1, or 2) or -N(R^4)- (wherein R^4 represents hydrogen or an alkyl group which may be substituted).)
(omitted)
[Claim 19] The preventive or therapeutic agent according to Claim 1, wherein the compound having calcium antagonistic action is selected from the group consisting of diltiazem hydrochloride, terodiline hydrochloride, nicardipine hydrochloride, barnidipine hydrochloride, flunarizine hydrochloride, verapamil hydrochloride, manidipine hydrochloride, cinnarizine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, nilzipin, nimodipine, penidipine, and benidipine.
(omitted)
[Claim 22] The preventive or therapeutic agent according to Claim 1, wherein the angiotensin II-mediated disease is hypertension."

(Indication 8B)
Paragraph [0006]

"Examples of a hydrocarbon group as R^1 include an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group, an aralkyl group, and the like, and an alkyl group, an alkenyl group, or a cycloalkyl group is preferable. The alkyl group as R^1 may be a linear or branched lower alkyl group having a carbon number of about 1 to 8, and examples of the alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like.
(omitted)"

(Indication 8C)
Paragraph [0012]

"Tautomers of the heterocyclic group (R^3) are as described below. (omitted) R^3 may be a carboxyl group, a tetrazolyl group, a trifluoromethanesulfonamide group (-$NHSO_2CF_3$), a phosphate group, a sulfonate group, a cyano group, or a lower (C_{1-4})alkoxycarbonyl group, or may be protected by a lower alkyl group or acyl group in which the above groups may be substituted, or may be a group which may form a negative ion under biological or physiological conditions (for example, by oxidation or reduction with enzyme in the body, or reaction in the body such as hydrolysis) or may chemically form the negative ion, or a group which may be changed into the negative ion."

(Indication 8D)
Paragraphs [0015] to [0017]

"[0015] In the general formula (I), examples of a carboxyl group as R^2 which may be esterified include formula -CO-D [wherein D represents a hydroxyl group or alkoxy which may be substituted {ex. a group in which an alkyl moiety is a hydroxyl group, a lower (C_{1-6})alkoxy group which may be substituted by amino which may be substituted (ex. amino, dimethylamino, diethylamino, piperidino, morpholino), halogen, lower (C_{1-6})alkoxy, lower (C_{1-6})alkylthio or dioxolenyl which may be substituted (ex. 5-methyl-2-oxo-1,3-dioxolen-4-yl), or a group represented by formula -O-CH(R^6)-OCOR^5, (omitted)}]. A substituent as R^2 may be a group which may form a negative ion or may be changed into the negative ion (ex. a tetrazolyl group, a trifluoromethanesulfonamide group, or a phosphate group or a sulfonate group which may be protected by alkyl (ex. lower (C_{1-4})alkyl) or acyl (ex. lower (C_{2-5})alkanoyl, benzoyl which may be substituted.)) [0016] Examples of substituent R^2 include -COOH and salt thereof, -COOMe, -COOEt, -COOtBu, -COOPr, pivaloyloxymethoxycarbonyl, 1-

(cyclohexyloxycarbonyloxy)ethoxycarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, acetoxymethoxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxycarbonyl, isobutyryloxymethoxycarbonyl, (1-ethoxycarbonyloxyethoxy)carbonyl, (1-acetoxyethoxy)carbonyl, (1-isobutyryloxyethoxy)carbonyl, cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, cinnamyloxycarbonyl, and cyclopentylcarbonyloxymethoxycarbonyl. R^2 may be a group which may form a negative ion (ex. COO-, a derivative thereof) under biological or physiological conditions (for example, by oxidation or reduction with an enzyme in the body, or reaction in the body such as hydrolysis) or may chemically form the negative ion, or a group which may be changed into the negative ion. R^2 may be a carboxyl group or a prodrug thereof. R^2 may be a group which may be biologically or chemically changed into a negative ion.

[0017] Among the above groups, it is preferable that R^2 is carboxyl, esterified carboxyl (ex. ester in which carbonyl is bound to methylester, ethylester or a group represented by formula -O-CH(R^6)-OCOR^5), or tetrazolyl, or carboaldehyde or hydroxymethyl which may be protected. In the general formula (I), a ring A may have a substituent other than a group represented by R^2, for example, halogen (ex. F, Cl, Br), cyano, nitro, lower (C_{1-4})alkyl, lower (C_{1-4})alkoxy, an amino group which may be substituted (ex. amino, N-lower (C_{1-4})alkylamino (ex. methylamino), N,N-di-lower (C_{1-4})alkylamino (ex. dimethylamino), N-arylamino (ex. phenylamino), alicyclic amino (ex. morpholino, piperidino, piperazino, N-phenylpiperazino)), formula -CO-D' [wherein D' represents a hydroxyl group or a group in which an alkyl moiety is a hydroxyl group, lower (C_{1-4})alkoxy which may be substituted by lower (C_{1-4})alkoxy, lower (C_{2-6})alkanoyloxy (ex. acetoxy, pivaloyloxy) or lower (C_{1-6})alkoxycarbonyloxy (ex. methoxycarbonyloxy, ethoxykarbonyloxy, cyclohexyloxycarbonyloxy)], or a tetrazolyl group, a trifluoromethanesulfonamide group, a phosphate group, or a sulfonate group which may be protected by lower (C_{1-4})alkyl or acyl (ex. lower (C_{2-5})alkanoyl, benzoyl which may be substituted, and lower (C_{1-4})alkyl, halogen or the like is preferable. At any position of the ring, one or two of these substituents may be simultaneously present."

(Indication 8E)
Paragraph [0029]
"Experimental Example 2
Antihypertensive action on spontaneously hypertensive rat (SHR) with calcium antagonist in combination

Compound 1: (±)-1-(cyclohexyloxycarbonyloxy)ethyl2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazol-7-carboxylate
MDP: manidipine
Methods: Six groups are set, each consisting of five 20-week male SHR per group. To each group, the compound 1 (0.1 or 1 mg/kg, p.o.) or MDP (3 mg/kg, p.o.) with single daily dose was orally administered, or both agents in combination with single daily dosing were orally administered, for 2 weeks. The blood pressure on the 1st, 7th, and 14th after the administration were non-invasively measured without use of an anesthetic.
Results: Results are shown in Table 2. Single dose of MDP (3 mg/kg/day, p.o.) exhibited clear antihypertensive action, and the compound 1 (0.1 and 1 mg/kg/day) had dose-dependently antihypertensive action. Antihypertensive action of the compound 1 was increased with MDP (3 mg/kg/day) in combination.

Administering the compound 1 (0.1 mg/kg) in the combination with MDP, antihypertensive action was more potent than or similar to administration of 1 mg/kg single dose of the compound 1. With combination of both agents, it can be expected that dose of each agent is reduced.
(omitted)"

Evidence A No. 9
(Indication 9A)
Lines 1 to 8 on page 127

"Development and application of angiotensin II-receptor antagonist (ARB) have been continued for several years, telmisartan, ibersaran, and olmesartan have been applied, and it is expected that the market of ARB is further revitalized. Regarding other antihypertensive agents, long-acting azelnidipine has been applied and this agent is added to the market of calcium antagonist of which the long-acting form is mainstream, as a novel antihypertensive agent.

Further, development of a purposeful combination drug of renin-angiotensin system antihypertensive agent and diuretic has been started. Although this agent is not strictly a novel drug, this development is worthy of attention as new development of novel drug."

(Indication 9B)
Lines 2 to 13 in the right column on 129
"3) Olmesartan [Sankyo]

Olmesartan is an imidazole skeleton-converted compound, and a prodrug in

which carboxylic ester is hydrolyzed in vivo so as to be the active form. In previous clinical trials, olmesartan has been found to have much more potent antihypertensive action than that of other AT1 receptor antagonists. Regarding this agent, domestic Phase III trial has been approved and is now applied.

As described above, new ARB will be added to the market after 2002, and it is thought that various efficacies are found based on clinical research."

(Indication 9C)
Line 15 to the last line in the left column on page 129

"Regarding calcium antagonists, long-acting agents such as amlodipine (amlodin; Sumitomo Pharma Co., Ltd., Norvasc; Pfizer Inc,) are mainstream, and have stable and potent antihypertensive action, and thus these agents have been used widely in Japan. Among these calcium antagonists, azelnidipine (Sankyo Co., Ltd. Ube Industries, Ltd.) has been applied. Azelnidipine is a dihydropyridinecalcium antagonist as shown in Fig. 2, and specifically binds to L-type calcium channel. Regarding blood kinetics, the maximum concentration time is about 3 hours and half-life is around 18 hours, and thus accumulation in body with long-term dosing was not observed; on the other hand, accumulation in body was observed in case of amlodipine. Phase III trial for this agent has been approved, and this agent will be added to the market as a novel calcium antagonist within several years. (omitted)"

(Indication 9D)
Lines 18 to 25 in the left column on page 130

"Although it was thought that the market of antihypertensive agents was reactivated with the development and arrival of ARB from the late 1990s to 2000, it is now difficult to expect to develop antihypertensive agents having new mechanism because of leading to the end of the development of ARB. It is thought to be necessary to collect evidences from large clinical trials regarding ARB mainly, and to pay attention to development of purposeful combination drugs such as ARB + diuretic."

Evidence A No. 10
(Indication 10A)
Fourth line from the bottom in the left column to line 3 in the right column on page 112S

"Olmesartan medoxomil in combination therapy

To reach target blood pressure recommended, a large trial showed that it is

required to administer a plurality of antihypertensive agents in combination. It was shown that in a case of administering olmesartan medoxomil in combination with another antihypertensive agent, this combination therapy has safety and efficacy."
(Indication 10B)
Fifth line from the bottom in the right column on page 112S to line 19 in the left column on page 113S

"Treat-to-Goal trial: In an open-label multicenter trial, single daily dosing 20 mg of olmesartan medoxomil to 201 patients with mild or moderate essential hypertension (average diastolic blood pressure in the sitting position of 95 to 110 mmHg) was performed for four weeks. After a 4-week interval, regarding patients whose blood pressure reached target pressure of ≤130/85 mmHg, therapy was switched to increase dose of olmesartan medoxomil to 40 mg/day, addition of HCTZ 12.5 mg/day, add amlodipine besylate of 5 mg/day, and increase dose of amlodipine besylate to 10 mg/day. Patients whose blood pressure reached the target blood pressure on any measured time point were removed from the trial. Co-primary endpoint was percentages of patients whose blood pressure reached the respective target blood pressures of ≤140/90 mmHg and ≤130/85 mmHg. Until 24-week, the blood pressure of 93.3% patients reached the target blood pressure of ≤140/90 mmHg, and the blood pressure of 87.7% patients reached the target blood pressure of ≤130/85 mmHg (Fig. 7) (reference 43; non-published data, Sankyo Co., Ltd., 2002). Further, the blood pressure of 95% patients reached target systolic blood pressure of ≤140 mmHg, and the blood pressure of 97.2% patients reached target diastolic blood pressure of ≤90 mmHg. These target blood pressures were recommended in the report from 6th joint national committee (JNC VI) regarding prevention, discovery, evaluation, and treatment of hypertension."

Evidence A No. 11
(Indication 11A)
Non-clinical outline (1) Pharmacodynamics, CS-866AZ 2.6.2 Outline of pharmacological test, page 11
"2.5 Antihypertensive action on SHR with orally 14-day repeated dose (4.2.1.1-5)

Methods: To male SHR (25-week, weight 307 to 410 g) in which a telemetry transmitter for measuring blood pressure was embedded in abdominal aorta, CS-866, CS-905 or CS-866AZ was orally administered in single daily repeated dose for 14 days. Before and after dosing period, respective observation periods of 7 days and 5 days are set, and only solvent was orally administered in single daily dose in the observation

period. Regarding 7 groups of solvent control group, low dose CS-866 administration group with single agent (0.2 mg/kg) and high dose CS-866 administration group with single agent (1 mg/kg), low dose CS-905 administration group with single agent (1.25 mg/kg) and high dose CS-905 administration agent with single agent (5 mg/kg), low dose CS-866AZ administration group (O/A=0.2/1.25 mg/kg) and high dose CS-866AZ administration group (O/A=1/5 mg/kg) (N=8, respectively) Note 1), blood pressure and heart rate were continuously measured from 3 days before administration, through the dosing period, and to the end of drug holidays. From the measured blood pressure and heart rate, 24-hr average blood pressure and 24-hr average heart rate on each dosing day were calculated. Changes in the day on 1st, 8th, and 14th of the administration were also observed.

Results: Changes in the day regarding blood pressure and heart rate on 1st day of the administration are shown in Fig. 2.6.2.2-5. In CS-866AZ administration group, blood pressure was gradually reduced after the administration in both low dose and high dose, the minimum blood pressure was 5 to 6 hours after the administration, and then blood pressure was gradually recovered. Over 2 to 11 hours after the administration in low dose CS-866AZ administration group, and 1 to 24 hours after the administration in high dose CS-866AZ administration group, the blood pressure was significantly reduced respectively, compared with the solvent control group. Similar changes were also observed on the 8th and 14th days of the administration. At 1 and 3 hours after the administration in low dose CS-866AZ administration group, and 1 to 7 hours after the administration in high dose CS-866AZ administration group, the heart rate was significantly increased respectively, compared with the solvent control group; on the other hand, the heart rate was not significantly increased on the 8th and 14th days of the administration.

Changes in 24-hr average blood pressure and heart rate are shown in Fig. 2.6.2.2-6. With any of CS-866 administration group with single agent, CS-905 administration group with single agent, and CS-866AZ administration group, the blood pressure was reduced from 1st day of the administration, compared with the solvent control group, and in a case of CS-905 administration group with low dose single agent, 24-hr average blood pressure was significantly reduced after the 6th day of the administration other than on the 8th day of the administration, and in a case of other administration groups, 24-hr average blood pressure was significantly reduced on all dosing days. Comparing each antihypertensive action with 24-hr average blood pressure, the descending order was high dose CS-866AZ administration group > high dose CS905 administration group with single agent > low dose CS-866AZ

administration group ≅ high dose CS-866 administration group with single agent > low dose CS-866 administration group with single agent > low dose CS-905 administration group with single agent, and thus it was recognized that antihypertensive action was increased with combined therapy. (omitted) As described above, antihypertensive action in administering CS-866AZ was gradually exhibited after the administration, was long-acting, was stable during the dosing period, and exhibited no tolerance. Rebound phenomenon of blood pressure with drug holidays was not observed. "

(Indication 11B)
Non-clinical outline (1) Pharmacodynamics, CS-866AZ 2.6.2 Outline of pharmacological test, page 13, FIG. 2. 6. 2. 2-6

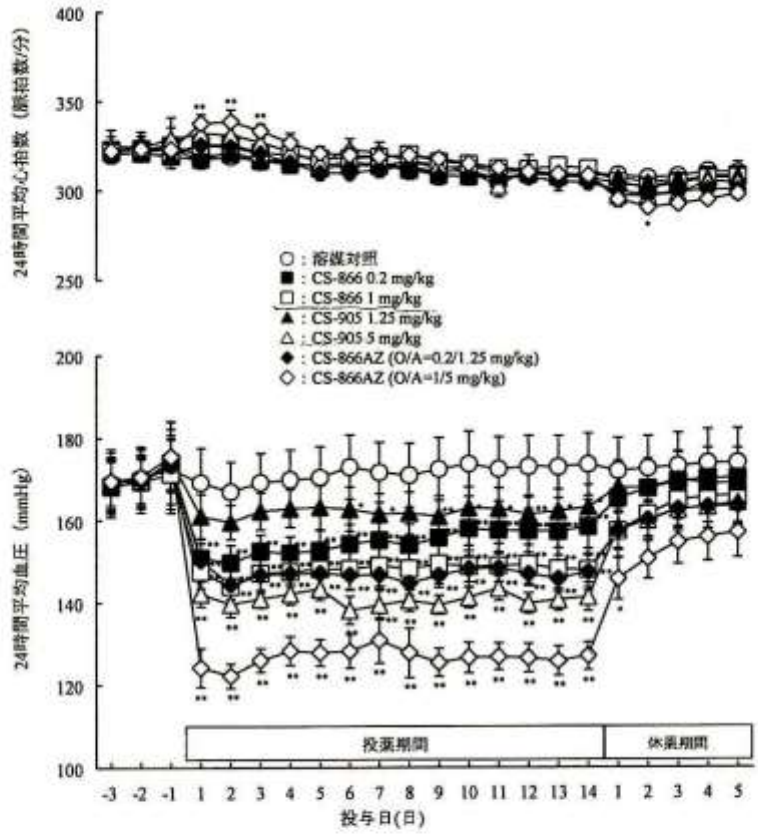


図 2.6.2.2-6 SHR に CS-866，CS-905，あるいは CS-866AZ を 14 日間反復経口投与した際の 24 時間平均血圧及び心拍数の推移（4.2.1.1-5）

平均値 ± 標準誤差，N=8

検定：溶媒対照群に対する Dunnett の多重比較検定 * $P<0.05$, ** $P<0.01$

２４時間平均血圧（ｍｍＨｇ） 24-hr average blood pressure (mmHg)
２４時間平均心拍数（脈拍数／分） 24-hr average heart rate (pulse rate/min)
溶媒対照 solvent control

投薬期間　　dosing duration
休薬期間　　drug holidays
投与日（日）　　administration day

図２．６．２．２－６ＳＨＲにＣＳ－８６６，ＣＳ－９０６，あるいはＣＳ－８６６ＡＺを１４日間反復経口投与した際の２４時間平均血圧及び心拍数の推移（４．２．１．１－５）　　Changes in 24-hr average blood pressure and heart rate in orally administering CS-866,CS-906 or CS-866AZ in repeated dose for 14 days (4.2.1.1-5)
平均値±標準誤差，N=8　average ± standard error, N=8
検定　test:
溶媒対照群に対する DUNNETT の多重比較検定　　multiple comparison test of DUNNETT for solvent control group

Evidence A No. 3-1
(Indication 3-1A)
14th line of preamble, and pages 83 to 101
It is described that at the start of creating guideline, more attention is paid "to include articles relating to hypertension in which Japanese are targeted as soon as possible", and 325 cited documents are presented.

Evidence A No. 6-1
(Indication 6-1A)
Abstract
"This invention relates to a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (omitted), and stroke, comprising a step of administering a therapeutically effective amount of (i) AT1-antagonist of valsartan or pharmaceutically acceptable salt thereof and (ii) a calcium channel blocker or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, to a mammal in need thereof, and to corresponding pharmaceutical combination composition."

(Indication 6-1B)
Paragraphs [0015] to [0017]
"[0015] The nature of hypertensive vascular diseases is multifactorial. Under certain

circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mechanisms of action does not necessarily lead to combinations with advantageous effects.
[0016] AT1 antagonist and CCB reduce intracellular calcium by different and complementary mechanisms and facilitate the vasodilator effects of nitric oxide, being particularly effective in reversing endothelium dysfunction.
[0017] All the more surprising is the experimental finding that the combined administration of the AT1-antagonist valsartan or pharmaceutically acceptable salt thereof and a calcium channel blocker or a pharmaceutically acceptable salt thereof results not only in a synergistic therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy and a broader variety of therapeutic treatment. This includes hemodynamic, antiproliferative, antithrombotic, and antiatherogenic properties."

(Indication 6-1C)
Paragraphs [0026] to [0027]
"[0026] Studies have been performed in SHR and demonstrate that the addition of CCB confers additional benefit over that of valsartan monotherapy. The area under the curve (AUC) for blood pressure reflects the changes in response to 6 week treatment in conscious SHR. Upon completion of the 6 week treatment period, hearts are removed for assessment of left ventricle mass and normalized to body weight.
[0027] The available results indicate an unexpected beneficial effect of a combination according to the invention."

(Indication 6-1D)
Scope of claims
"1. A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (omitted), and atherosclerosis and stroke comprising a step of administering a therapeutically effective amount of (i) AT1-antagonist of valsartan or pharmaceutically acceptable salt thereof and (ii) a calcium channel blocker or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, to a mammal in need thereof.
(omitted)
4. A pharmaceutical combination composition comprising a therapeutically effective amount of (i) AT1-antagonist of valsartan or a pharmaceutically acceptable salt thereof and (ii) a calcium channel blocker or pharmaceutically acceptable salt thereof and a

pharmaceutically acceptable carrier.
5. The pharmaceutical combination composition of claim 4, wherein the pharmaceutical combination composition is for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, hypertension, (acute and chronic) congestive heart failure, (omitted), myocardial infarction and after effect thereof, atherosclerosis, angina pectoris (regardless of unstable or stable), (omitted), and stroke.
6. The pharmaceutical combination composition of claim 4, wherein the pharmaceutical combination composition comprises the calcium channel blocker selected from the group consisting of amlodipine, (omitted), or a pharmaceutically acceptable salt thereof.
7. The pharmaceutical combination composition of claim 4, wherein the pharmaceutical combination composition comprises amlodipine or a pharmaceutically acceptable salt thereof.
(omitted)"

Evidence A No. 12
(Indication 12A)
Lines 1 to 6 on page 151

"Although Dahl salt-sensitive hypertensive rats have hypertension with renal tabular damage, Dahl alleged that this salt-sensitive hypertensive rat is an essential hypertensive model. However, it has recently been thought that Dahl salt-sensitive hypertensive rats have hypertension with salt overeating or renal hypertension with tabular damage."

(Indication 12B)
Third line from the bottom in the left column to line 27 in the right column on page 156
"8.4 Utilization of animal model for development of antihypertensive agents

In secondary hypertension, removal of vasopressor principle is possible. Secondary hypertensive therapy is performed by removing this vasopressor principle from a living body. That is, hypertension with salt overeating reduces intake of salt, hypertension with obesity reduces intake of lipids and saccharides, thereby removing obesity. (omitted) These have antihypertensive action from hypertension to normal blood pressure. Secondary hypertension is completely cured by these therapies.

In essential hypertension, removal of vasopressor principle, major gene, and replacement of systematic arterial smooth muscle are impossible. Thus, removal of essential hypertension is performed by administering antihypertensive agent. (omitted)

Development of antihypertensive agents means development of antihypertensive

agents for lowering hypertension of essential hypertension. Thus, a newly developed agent is administered to a spontaneously hypertensive rat SHR being an animal model for essential hypertension, and the antihypertensive action is determined. An agent acts on arterial smooth muscle of SHR, and antihypertensive effects of agent in cellular or molecular unit, such as effect for inhibiting contraction of arterial smooth muscle of SHR and effect for promoting relaxation of arterial smooth muscle of SHR, are researched. Taking these results into consideration, a novel antihypertensive agent is developed. The antihypertensive agent is used for clinical practice of essential hypertension."

(Indication 12C)
Lines 14 to 18 in the left column on page 157

"An animal model for human essential hypertension corresponds to a spontaneously hypertensive rat (SHR), an animal model for human secondary hypertension corresponds to a Dahl salt-sensitive hypertensive rat, (omitted)."

Evidence A No. 13
(Indication 13A)
Lines 4 to 6 in the right column on page 191

"Nearly 90% of hypertension in Japan is called essential hypertension, and the cause cannot be specified."

(Indication 13B)
Lines 20 to 23 in the right column on page 192

"It was estimated that apoE KO mice did not become hypertensive when feeding normal diet, but became hypertensive when developing arteriosclerosis due to cholesterol loading."

Evidence A No. 14
(Indication 14A)
Outline on page 99
"OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, and adverse effects of olmesartan medoxomil, an angiotensin receptor II-antagonist, for the treatment of hypertension.
DATA SOURCES: Information was obtained from MEDLINE search (1996 to April, 2002) of English-language medical literature. (omitted)

STUDY SELECTION: All articles identified from data sources with pertinent information regarding olmesartan medoxomil were evaluated, and all pieces of information deemed relevant were included in this review.
DATA SYNTHESIS: Olmesartan medoxomil is a competitively priced addition to the class of angiotensin II-receptor antagonists. Monotherapy with olmesartan medoxomil in once-daily doses of 20 to 40 mg has produced significant reductions in systolic and diastolic blood pressure in patients with hypertension. Adverse effects have been minimal with olmesartan medoxomil, with dizziness being the only adverse effect occurring more often than with placebo in clinical trials. Additionally, animal studies indicate that olmesartan medoxomil may prove to be useful treatment for diabetic nephropathy, as well as atherosclerosis.
CONCLUSIONS: Olmesartan medoxomil has a favorable safety and efficacy profile, with blood pressure-lowering effects comparable to those of other angiotensin receptor blockers (i.e., losartan, valsartan, irbesartan). At this time, formulary decisions will be driven primarily by economic issues. Theoretical benefits of olmesartan medoxomil in reducing atherogenesis and lowering angiotensin II concentrations better than the alternative agents will be determined only with more extensive research.
(omitted)"

(Indication 14B)
Lines 16 to 30 in the left column on page 100

"In test for examining effect of olmesartan medoxomil on crab-eating macaque with diet induced hyperlipidemia, effect of the agent on vascular endothelium was studied. In the aortic arch, olmesartan medoxomil significantly reduced accumulation of fatty streak, area of atherosclerotic damage, and intimal thickening. Although blood pressure and concentration of serum cholesterol were not changed during treatment, these changes occurred. These pieces of information show that olmesartan medoxomil has possibility to have favorable action on vascular endothelium, independently of the antihypertensive action. It is thought that anti-atherosclerotic effects of olmesartan on growth factors, inhibition of chemokine and adhesion molecules, migration inhibition of macrophage to intima, and migration of endothelial damage are secondary actions."

(Indication 14C)
Lines 34 to 48 in the right column on page 103

"Abstract In clinical research for safety and efficacy, olmesartan medoxomil being the latest ARB added to the market of antihypertensive agents, had favorable

action. Data on pharmacodynamics and pharmacokinetics support once-daily dose, and it is suggested that effect on diastolic blood pressure may be more potent than effect with dose corresponding to other ARB. (omitted) Since there is not relatively severe adverse effects or drug interactions relating to short and long-term dosing, this agent is a desirable option in hypertensive therapy."

Evidence A No. 14-1

Evidence A No. 14-1 is part of translation of Evidence A No. 14, and is substantially the same as Indications 14A to 14C of Evidence A No. 14.

Evidence A No. 14-2
(Indication 14-2A)
Page 6

Evidence A No. 14-2 is a list of documents issued on January 1, 2003, a document regarding Evidence A No. 14 is described on page 6.

Evidence A No. 15
(Indication 15A)
Line 1 to last line in the left column on page 721

"Hypertension, ischemic heart disease, and cerebral circulatory disturbance involve arteriosclerosis as basic lesion, and it is thought that the development of arteriosclerosis is one of the factors to have adverse effect on clinical condition. There have been numerous reports to show that calcium antagonists have action for inhibiting arteriosclerosis[2-5)] since Henry proved the action in an experiment using nifedipine in 1981[1)]. Azelnidipine is a long-acting calcium antagonist of dihydropyridine, the action is slowly exhibited, and thus activation of sympathetic nerve system or renin-angiotensin system hardly occurs and it is expected to have effect on organ protection[6-8)]. Further, this agent has high lipophilicity[9)] and transitivity to vascular walls[7, 8)], and thus it is expected to have effect especially on arteriosclerosis. In this report, using high cholesterol loading rabbits, anti-atherogenic action of azelnidipine was examined."

(Indication 15B)
Paragraph 1 in the left column on page 726

"Anti-atherogenic action of azelnidipine was examined using a model for arteriosclerosis of the aorta made by a high cholesterol loading rabbit. The results clearly indicate that a ratio of the lesion area of aorta was significantly decreased by

administering azelnidipine, and the accumulation of cholesterol or Ca in the aorta wall, which is increased with the development of the aorta, was inhibited. However, azelnidipine did not have effect on total serum cholesterol or lipoprotein, and it is thought that anti-atherogenic action with azelnidipine is induced by a mechanism different from lipid reduction in the blood. It has been reported that other calcium antagonists inhibit the aorta in experiments using the same arteriosclerosis model, without affecting serum lipid [1, 3-5)]."

(Indication 15C)
Paragraph 2 in the right column on page 726

"As described in the previous report[8)], azelnidipine is a calcium antagonist which is called third-generation and has antihypertensive action similar to that of amlodipine; on the other hand, azelnidipine has higher affinity to vascular tissue than that of amlodipine[7, 8)], and has high lipophilicity[9)]. According to Masumoto et al.[9)], partition coefficient (Log PHPLC), being an indicator for lipophilicity, of amlodipine is 3.95, and that of azelnidipine is 5.18, and thus it can be said that lipophilicity of azelnidipine is 1.7 times that of amlodipine. In fact, it has been shown that azelnidipine has high binding to lipoprotein (Ikeda et al., non-published data). Azelnidipine having such a property is expected to have usefulness for arteriosclerosis, especially among similar agents."

Evidence A No. 16
(Indication 16A)
Paragraph 1 in the left column on page 703

"Azelnidipine (CS-905) is a novel dihydropyridine calcium antagonist which was developed so as to have long-acting action and slow onset of action[1-4)] (The chemical structure is shown in Fig. 1). In this report, Ca antagonistic action of azelnidipine was examined in a receptor binding test and a test using an isolated vessel, and the action was compared with those of similar agents, especially amlodipine."

(Indication 16B)
Paragraph 3 in the right column on page 708

"As described above, this study showed that azelnidipine had slow and long-acting action in vascular level, and the properties were more excellent than those of similar agents such as amlodipine. These properties are thought to be associated with high lipophilicity and vascular affinity of the agent."

Evidence A No. 17

(Indication 17A)

Last line in the right column on page 711 to line 5 in the left column on page 712

"In this report, antihypertensive action of azelnidipine on SHR was compared with those of similar agents (second-generation and third-generation calcium antagonists), and relation between antihypertensive action and pharmacokinetics, especially in vascular affinity of the agent, was examined."

(Indication 17B)

Line 14 in the left column to line 2 in the right column on page 717

"However, azelnidipine has mild tachycardia compared with amlodipine whose antihypertensive action is very similar to that of azelnidipine, and it is suggested that effects of the two agents on heart rate are qualitatively different."

(Indication 17C)

Paragraph 2 in the left column on page 719

"As described above, azelnidipine has slow and long-acting antihypertensive action, and hardly causes the activation of tachycardia or renin-angiotensin system based on activation of the sympathetic nervous system. Amlodipine has similar antihypertensive action to these agents, while it is thought that azelnidipine has high vascular affinity and lipophilicity, leading to the antihypertensive action. It is expected that azelnidipine having such a property has an excellent effect on organ protection."

Evidence A No. 18

(Indication 18A)

Seventh line from the bottom to the last line in the left column on page 2401

"Antihypertensive agents having possibility to causing adverse effect on arteriosclerosis

1. Diuretic

Total cholesterol and neutral fat are increased and HDL-Cholesterol is decreased with any of thiazide diuretic and loop diuretic. Thus, it is thought that they have negative effect on arteriosclerosis."

Evidence A No. 19

(Indication 19A)

Line 5 in the right column on page 63 to line 4 in the left column on page 64

"1. Diuretics

Diuretics have been first-line antihypertensive agents in the past; on the other hand, it has been reported that this agent especially increases thiazide, triglyceride, and LDL-cholesterol. However, it has been reported that this abnormal lipid metabolism is weakened or diminished in long-term therapy. On the other hand, it has been thought that a K-sparing diuretic has comparatively less effect on serum lipids. Regarding insulin sensitivity, it has been known that diuretics, especially thiazide diuretics, have adverse effect on glycometabolism."

Evidence A No. 20
(Indication 20A)
Paragraph [0002]

"[Industrial Application Field] The present invention relates to imidazole-5-carboxylic acid derivatives having excellent angiotensin II (hereinafter referred to as AII) antagonistic action and action for lowering blood pressure."

(Indication 20B)
Paragraph [0204]
"Example 61

4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(tetrazol-5-yl)phenyl]phenyl}methylimidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl ester (Exemplary compound No. 2-17)
(a) 4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazol-5-yl)phenyl]phenyl}methylimidazole -5- carboxylic acid (5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl ester

To 0.97 g of potassium carbonate in 100 mL of N,N-dimethylacetamide heated to 60°C, 1.14 g of 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxolane-4-yl)methyl ester obtained in Reference Example 31 and 2.35g of benzyl bromide in 50 mL of N,N-dimethylacetamide were added while stirring. The mixture was stirred at 60°C for 3.5 hours, then ethyl acetate was added, and an ethyl acetate layer was separated. The ethyl acetate layer was washed, then dried on anhydrous magnesium sulfate, and the solvent was removed. The residue was subjected to silica gel column chromatography using hexane-ethyl acetate (1:1) as a solvent, and 1.4 g of a foamy solid target compound was obtained. Further, this compound was crystallized in diisopropyl ether.
Melting point: 98-99°C (degraded).

NMR spectrum (CDCl3) δ ppm: 0.89 (3H, t, J=7.5 Hz), 1.62 (6H, s), 1.6-1.75 (2H, m), 1.97 (3H, s), 2.54 (2H, t, J=8 Hz), 4.70 (2H, s), 5.30 (2H, s), 5.61 (1H, s), 6.68 (2H, d, J=7.5 Hz), 6.90-7.52 (20H, m), 7.87 (1H, d, J=7.5 Hz).
(b) 4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(tetrazol-5-yl)phenyl]phenyl}methylimidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl ester

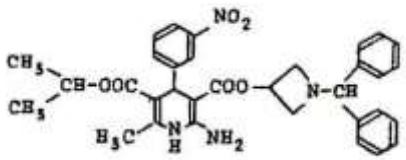
1.4 g of 4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazol-5-yl)phenyl]phenyl}methylimidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl ester obtained in Example 61(a) in 48 mL of 75% aqueous acetate was heated to 60°C and stirred for 1 hour, and then the reaction liquid was concentrated. The process in which the residue was dissolved in toluene and then concentrated was repeated, and after removing residual acetate and water, the residue was subjected to silica gel column chromatography using methanol-dichloromethane (1:9 and 1:4) as a solvent, and 0.73 g of a crystalline target compound was obtained.
Melting point: 170-172°C.
NMR spectrum (CDCl3) δ ppm: 0.93 (3H, t, J=7.5 Hz), 1.63 (6H, s), 1.6-1.8 (2H, m), 2.19 (3H, s), 2.70 (2H, t, J=7.5 Hz), 5.00 (2H, s), 5.45 (2H, s), 6.83 (2H, d, J=8 Hz), 7.10 (2H, d, J=8 Hz), 7.42-7.63 (3H, m), 7.83 (1H, dd, J=1, 7.5 Hz)."

Evidence A No. 21
(Indication 21A)
6th line from the bottom in the right column on page 1 to line 5 in the left column on page 2
"Purpose of the present invention

The present inventors have synthesized dihydropyridine derivatives to develop cardiovascular agents, performed the pharmacological test, and examined the correlation between the structure and action, and have shown that a compound, of the present invention, having the following general formula (I) has pharmacological action such as calcium antagonistic action, antihypertensive action, asodilator action, action for improving hyperlipidemia and action for inhibiting the production of lipid peroxide, has low toxicity, and is useful as a medicament for treating circulatory system diseases such as hypertension and angina pectoris, whereby they have accomplished the present invention."

(Indication 21B)
6th line from the bottom in the right upper column on page 10 to line 7 in the left

column on page 11
"Example 1
2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(1-benzhydryl-3-azetidinyl)ester 5-isopropyl ester and dihydrochloride thereof



To 1.39g (0.005 mol) of 2-(3-nitrobenzylidene)acetoacetic acid isopropyl ester and 1.62g (0.005 mol) of amidinoacetic acid(1-benzhydryl-3-azetidinyl)acetic ester in 80 mL of isopropyl alcohol, 0.27g (0.005 mol) of sodium methylate was added and the mixture was heated and refluxed for 4 hours. After cooling, all insoluble matters were removed, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, and dried on anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was subjected to silica gel column chromatography (toluene : ethyl acetate = 3:1), and a light yellow crystalline target substance (educt) was obtained.
Yield: 2.17g (74%)
Melting point: 95 to 98°C
(omitted)

To 0.87g of educt obtained as described above, in 20 mL of chloroform solution, hydrogen chloride was injected for 5 minutes. The solvent was removed under reduced pressure, and a light yellow crystalline target substance (dihydrochloride) was obtained.
Yield: 0.95g
Melting point: 118 to 120°C
(omitted)"

5-2. Described matters in respective items of Evidence B

The descriptions of Evidence B No. 3, B No. 12, and B No. 13 are follows.

Evidence B No. 3
(Indication B No. 3A)
Lines 18 to 38 in the right column on page 146
"RESULTS
Effect of combination of ARB with various CCBs on neointimal formation after cuff

placement

Cuff placement around the femoral artery induced neointimal formation (Fig. 1). In our previous studies, an ARB or CCB alone was shown to inhibit neointimal formation. Moderate and high dose of each CCB alone inhibited the neointimal formation (see Supplementary Fig. S1 online). On the other hand, a low dose of nifedipine (1.0 mg/kg/day), amlodipine (0.1 mg/kg/day), and azelnidipine (0.1 mg/kg/day) did not affect neointimal formation (see Supplementary Fig. S1 online). In this study, we used each drug at a subeffective dose, by which neointimal formation could not be significantly inhibited. Each combination of olmesartan with a CCB, nifedipine, amlodipine, or azelnidipine, at subeffective dose significantly inhibited neointimal formation (Fig. 1). However, this inhibitory action of the combination was greatest for olmesartan with azelnidipine. On the other hand, a combination of olmesartan and a subeffective dose of HCTZ did not significantly change neointimal formation (Fig. 1). These combinations did not change the systolic blood pressure (Table 1)."

(Indication B No. 3B)
Figure 1b on page 147
"

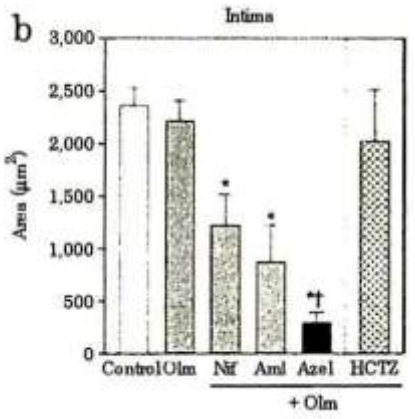


Figure 1 Effect of Olm with calcium channel antagonist on neointimal formation in injured artery 14 days after placing polyethylene cuff

An artery sample was taken out 14 days after placement of the cuff, and the paraffin embedded sections were prepared. ... (b) Sectional area of intima is described in Methods. Each group is n=5 to 7. Values are average ± deviation. Aml, amlodipine

(0.1 mg/kg/day); Azel, azelnidipine (0.1 mg/kg/day); HCTZ, hydrochlorothiazide (0.5 mg/kg/day); Nif, nifedipine (1.0 mg/kg/day); Olm, olmesartan (0. 5mg/kg/day). *P<0.05 vs. control or Olm+HCTZ. †P<0.05 vs. Olm + Nif or Olm + Aml."

Evidence B No. 12
(Indication B No. 12A)
Lines 6 to 16 on page 36

"Synergetic effect means that combination of the two agents has significant effect compared with addition of effects of respective agents. To analyze these pieces of data, the authors use the Dunnet test in three times of comparison with a control group; however, the test cannot directly evaluate synergetic effect. To directly evaluate synergetic effect, the following analysis should be done. This test is a factorial experiment (2×2) in which an agent A is 2 doses and an agent B is 2 doses, and thus two-way analysis of variance (ANOVA) should be used. In analysis of variance, synergetic effect can be evaluated with F-test regarding interaction of agents A and B. If the interaction is significant, it shows that the synergetic effect is present. If the interaction is not significant, it means that the effect of two agents is additive, rather than synergetic."

Evidence B No. 13
(Indication B No. 13A)
Supplemental figure S1

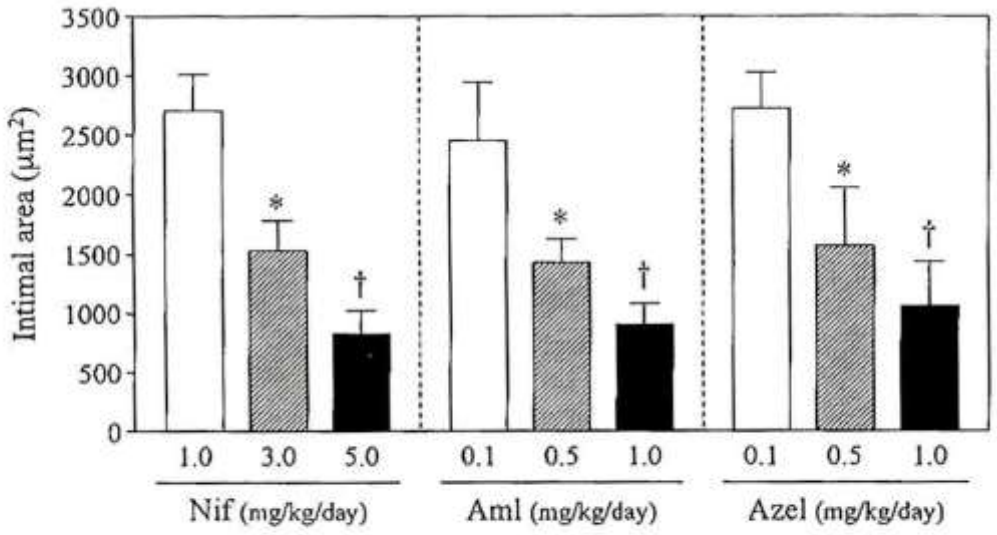


Figure 1

6. Judgment by the body

It is judged by the body that the patent according to the Corrected inventions of cases 6 to 25 cannot be invalidated based on the Reasons for invalidation 1 and 2. The reasons are as follows.

6-1. Regarding Reasons for invalidation 1

(1) Regarding corrected invention of case 6

A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected invention of case 6 is the following (a) to (f).

(a) From the described matters of Indication 8A of Evidence A No. 8, the invention of "an agent for the prevention and/or treatment of hypertension, wherein the agent comprises a compound or salt thereof which is represented by the general formula (I) according to Claim 1 and has antagonistic action of angiotensin II, and manidipine hydrochloride in combination." (hereinafter referred to as the "Invention A-8") is described in Evidence A No. 8.

(b) Comparing the Corrected invention of case 6 with the Invention A-8, the corresponding features and different features are as follow.

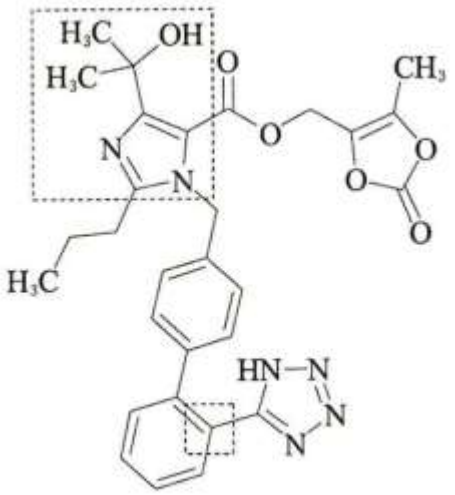
<Corresponding features>

Both inventions relate to a medicament for the prevention and/or treatment of

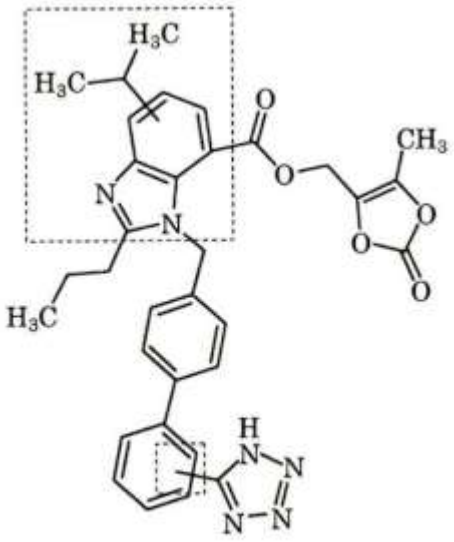
hypertension, wherein the medicament comprises angiotensin II-receptor antagonist and calcium antagonist as active ingredients.

<The different features>

In the case of the Corrected invention of case 6, the angiotensin II-receptor antagonist is "olmesartan medoxomil," but on the other hand, in the case of the Invention A-8, the angiotensin II-receptor antagonist is "A-8 ARB"; and the calcium antagonist is "azelnidipine" in the case of the Corrected invention of case 6, but on the other hand, in the case of the Invention A-8, the calcium antagonist is "manidipine hydrochloride." (olmesartan medoxomil)



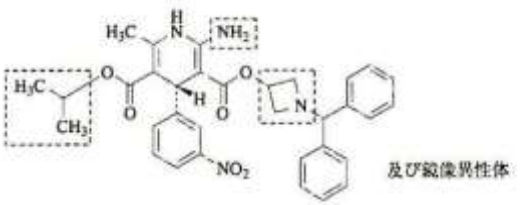
（オルメサルタン メドキソミル）



（甲８ＡＲＢ）

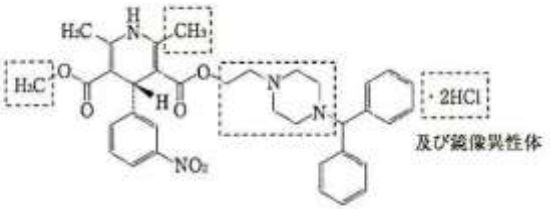
（オルメサルタン　メドキソミル）　(olmesartan medoxomil)

（甲８ＡＲＢ）　(A-8 ARB)



及び鏡像異性体

（アゼルニジピン）



及び鏡像異性体

（塩酸マニジピン）

（アゼルニジピン）　(azelnidipine)

及び鏡像異性体　and enantiomer

（塩酸マニジピン）　　(manidipine hydrochloride)

(c) Although each of the angiotensin II-receptor antagonist and calcium antagonist used do not completely correspond between the Corrected invention of case 6 and the Invention A-8, it can be said that the two inventions use compounds that are similar in structure.

As described in state of the art as of the priority date of the Patent, using angiotensin II-receptor antagonist and calcium antagonist in combination was known to possibly exhibit excellent additive or synergetic effect at the time (Evidence A No. 3), and on the basis of the knowledge, combinations of various angiotensin II-receptor antagonists and calcium antagonists have been used as described in Evidence A No. 4 to A No. 7.

Under such conditions, replacing the "angiotensin II-receptor antagonist" with "olmesartan medoxomil" having a structure similar to A-8 ARB and replacing the "calcium antagonist" with "azelnidipine" having a structure similar to manidipine hydrochloride, for the purpose of exhibiting synergetic effect, would have been easily conceived by a person skilled in the art having access to the description of Evidence A No. 8 which discloses the invention of the agent comprising the compound which is represented by general formula (I) according to Claim 1 and has antagonistic action of angiotensin II, and manidipine hydrochloride in combination.

Thus, the Corrected invention of case 6 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 8.

(d) As of the priority date of the Patent, olmesartan as a novel angiotensin II-receptor antagonist (ARB) and azelnidipine as a novel calcium antagonist have been respectively applied, it was thought that it was difficult to expect development of antihypertensive agents having a new mechanism, and the development of purposeful combination drugs, such as ARB + diuretic was worthy of attention as new development of novel drug (Evidence A No. 9). It is also described in Evidence A No. 9 that olmesartan has much more potent antihypertensive action than that of other AT1 receptor antagonists, and accumulation of azelnidipine in the body with long-term dosing is not observed, but on the other hand, accumulation in body is observed in the case of amlodipine, and thus it is clear that a person skilled in the art having access to the description of Evidence A No. 9 is strongly motivated to replace the "angiotensin II-receptor antagonist" and "calcium antagonist" in Evidence A No. 8, with "olmesartan" and "azelnidipine" which are

expected to be added to the market in the future.

Thus, the Corrected invention of case 6 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 8, taking Evidence A No. 9 into consideration.

(e) Since olmesartan medoxomil already had possibility to be useful for treating atherosclerosis with the animal experiment (using crab-eating macaques with diet induced hyperlipidemia) and it has been thought that the effect is independent of the antihypertensive action, this agent has been thought to be a more favorable agent than other ARBs (e.g. losartan, valsartan, irbesartan) (Evidence A No. 14). Further, azelnidipine had been thought to have usefulness especially for arteriosclerosis, since the agent has higher affinity to vascular tissue and lipophilicity, compared with amlodipine which is a typical third-generation calcium antagonist and had often been formulated as of the priority day for the Patent (Evidence A No. 15 to A No. 17).

In addition, since arteriosclerosis is a disease closely associated with hypertension and better antihypertensive action is expected if arteriosclerosis can be treated simultaneously, when using a combination of ARB and calcium antagonist in treatment of hypertension, it is easy to select "olmesartan medoxomil" as the ARB and select "azelnidipine" as the calcium antagonist.

Thus, the Corrected invention of case 6 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 8, taking Evidence A No. 9 and A No. 14 to A No. 17 into consideration.

(f) Considering that, as of the priority day for the Patent, it had been well known from Evidence A No. 3 that using the angiotensin II-receptor antagonist and calcium antagonist in combination is expected to have excellent effect (additive or synergetic effect), it cannot be acknowledged that the Corrected invention of case 6 has an "advantageous effect" useful to positively acknowledge the presence of inventive step.

In addition, it cannot be confirmed that the combination group exhibits the synergetic effect, referring the effect described in the Description of the case. That is to say, the antihypertensive action of the combination group is only described in Example 2 of the Description of the case, and it cannot be determined whether the antihypertensive action is more excellent than that of the monotherapy group, and taking into consideration Evidence A No. 11 in which substantially the same experimental result is described, it cannot be acknowledged that the action has more additive effect. Further, it is acknowledged by the demandee in the written reply (page

49) that the results of Example 2 correspond to the results of Fig. 2.6.2.2-6 in Evidence A No. 11 and the action does not have more additive effect.

Further, it is described in Example 3 of the Description of the case that animal models for hyperlipidemia is used, the same amount of each agent is used in the monotherapy group and combination group, and the standard error is large, and it cannot be acknowledged that from the experimental results of Example 3, the combination group exhibits synergetic antihypertensive action, compared with monotherapy.

Incidentally, during procedures to apply for the Patent, certified experiment results were submitted on June 14, 2006. From the data described in the certified experiment results, it has been understood that the combination group exhibited synergetic effect in antihypertensive test using Dahl salt-sensitive hypertensive rats, animal models for secondary hypertension. These experimental results are different from those of the experiment for essential hypertension described in the Description of the case as examined above, and considering the point that the synergetic effect was obtained from the experiment for secondary hypertension and the point that the these experimental results were data to appeal an effect more excellent than the effect described in Example 2 of secondary hypertension, the synergetic effect should not be regarded as the effect of the Corrected invention of case 6 for which hypertension is a target disease.

B However, according to the below reasons, it is judged by the body that the Patent according to the Corrected invention of case 6 cannot be invalidated based on the Reasons for invalidation 1.

Regarding (c)

The compound (A) of the Corrected invention of case 6 is "olmesartan" of angiotensin II-receptor antagonist, and the compound (B) is "azelnidipine" of calcium antagonist. However, olmesartan is not described in Evidence A No. 8. Olmesartan is not a compound included in the compounds represented by general formula (I) of the Invention A-8. Further, azelnidipine is also not described in Evidence A No. 8. Thus, for a person skilled in the art having access to the description of Evidence A No. 8, to make the Corrected invention of case 6 based on the Invention A-8, the person skilled in the art firstly has to combine the selections of substituents in the compound represented by general formula (I) of Invention A-8 and having antagonistic action of angiotensin II-receptor, has to understand A-8 ARB not specifically described in Evidence A No. 8, has to think of the chemical structure of olmesartan based on the chemical structure of

A-8 ARB and the use of olmesartan instead of A-8 ARB, has to think of the chemical structure of azelnidipine based on the chemical structure of manidipine and the use of azelnidipine instead of manidipine hydrochloride, and has to develop a production method of olmesartan and azelnidipine.

However, for the person skilled in the art having access to the description of Evidence A No. 8, to think of and actually implement the above idea, even though the person skilled in the art has common general technical knowledge described in Evidence A No. 3 and Evidence A No. 4 to A No. 7, alleged by the demandant, regarding the attempt of combination of angiotensin II-receptor antagonists, such as telmisartan, eprosartan and valsartan, and calcium antagonists (Indications 3A to 3D, 4A to 4C, 5A, 6A, 7A), it can be acknowledged that various instances of inventiveness and trial and error are required, and thus it cannot be said that the person skilled in the art would have been able to think of and actually implement the above idea without requiring particular inventiveness.

Regarding (d)

As indicated in Indications 9A and 9C, it is described in Evidence A No. 9 that azelnidipine is the calcium antagonist which has been applied. Since manidipine hydrochloride is described in Evidence A No. 8 as one of the calcium antagonists (Indication 8A), even though a person skilled in the art having access to both Evidence A No. 8 and A No. 9 would have been able to use azelnidipine described in Evidence A No. 9 as one of the calcium antagonists, instead of manidipine hydrochloride of the Invention A-8, without requiring particular inventiveness, it cannot be said that the person skilled in the art would have been able to use olmesartan described in Evidence A No. 9, without requiring particular inventiveness, instead of the compound represented by formula (I) and specified as the angiotensin II-receptor antagonist used in the Invention A-8, which is different in chemical structure from olmesartan, even though olmesartan is described in Evidence A No. 9 as an angiotensin II-receptor antagonist which has been applied and the person skilled in the art has common general technical knowledge alleged by the demandant.

Regarding (e)

The indication in the above (d) is not changed even though a person skilled in the art has access to Evidence A No. 14 to A No. 17 in which it is described that olmesartan or azelnidipine has effect on arteriosclerosis.

Regarding (f)

In Example 2 of the Description of the case, entitled "Antihypertensive action," it is clear that using olmesartan medoxomil and azelnidipine in combination exhibits antihypertensive action in spontaneously hypertensive rats SHR. For this reason, it can be said that it is clear in the Description of the case that the medicament according to the Corrected invention of case 6 exhibits antihypertensive action in patients with spontaneous hypertension.

It is also described in Example 3 of the Description of the case, entitled "Antihypertensive action," that a high fatty diet (containing 0.15% cholesterol and 15% unsalted butter) was given to ApoE knockout mice following the start of administering an agent, and the agent was orally administered to animals for 24 successive weeks. As the experimental results, it is described that systolic blood pressure after 21 to 24 hours into administration at 23rd week, of the olmesartan medoxomil administered group, azelnidipine administered group, olmesartan and medoxomil + azelnidipine combination group was 121±4, 127±4, and 112±3 mmHg in this order, and blood pressure was 8, 2, 17 mmHg lower than that of control group (129±3 mmHg) (Table 3). Further, regarding the experimental results, in two-way analysis of variance, it is described in the end of Example 3 that it could be acknowledged that the olmesartan medoxomil + azelnidipine combination group exhibited significant antihypertensive action compared with the monotherapy group, and the effect was synergetic effect compared with the monotherapy group. The two-way analysis of variance is an analysis for evaluating synergetic effect of interaction in using agents in combination (Indication B No. 12A), and thus it can be said that it is clear in Example 3 of the Description of the case that the olmesartan medoxomil + azelnidipine combination group exhibits synergetic antihypertensive action in ApoE knockout mice given the high fatty diet. Thus, it can be said that it is clear in the Description of the case that the medicament according to the Corrected invention of case 6 exhibits synergetic antihypertensive action in patients with hyperlipidemia. Further, the high fatty diet includes 0.15% cholesterol, as described above, considering that ApoE knockout mice are experimental animals that become hypertensive when developing arteriosclerosis due to cholesterol loading (Indication 13B), it is shown that ApoE knockout mice become hypertensive. Thus, it is shown in Example 3 that it is clear that using olmesartan and azelnidipine in combination exhibits synergetic antihypertensive action in mice with hypertension due to the high fatty diet. For this reason, it can be said that it is clear in the Description of the case that the medicament according to the Corrected invention of case 6 exhibits synergetic antihypertensive action in patients with hyperlipidemia, arteriosclerosis, and

hypertension.

In addition, it is described in Example 1 of the Description of the case, entitled "Action for inhibiting arteriosclerosis," that using azelnidipine and olmesartan in combination in cuff-induced vascular damage model mice inhibited the proliferation of vascular smooth muscle cells and exhibited action for improving remodeling of the vessel. Thus, it can be said that it is clear in the Description of the case that the Corrected invention of case 6 has action for inhibiting arteriosclerosis by action for remodeling of the vessel, as well as antihypertensive action. Further, it is described in the above Example 1 that "When 0.1 mg/kg/day of azelnidipine and 0.5 mg/kg/day of olmesartan (neither of these drugs elicited any significant effects at these doses) were administered to wild type mice at the same time, the increase in DNA synthesis of vascular smooth muscle cells and potentiation of neointimal formation in the blood vessels were significantly suppressed (FIG. 5 and 6). From these results, it was clearly demonstrated in vivo that using azelnidipine and olmesartan in combination works synergistically, inhibits proliferation of the vascular smooth muscle cells, and improves vascular remodeling." and "The synergistic action of azelnidipine and olmesartan described above was investigated in an in vitro study. As shown in FIG. 7, facilitation of DNA synthesis in cultured rat vascular smooth muscle cells following stimulation by angiotensin II was suppressed by administration of azelnidipine in a concentration-dependent manner. When low doses of azelnidipine and olmesartan insufficient to elicit any effects alone were co-administered, DNA synthesis of cultured rat vascular smooth muscle cells was significantly suppressed (FIG. 8).", and it can be said that it is clear that using olmesartan and azelnidipine in combination exhibits synergetic action for improving remodeling of the vessel. For this reason, it can be said that it is clear in the Description of the case that the medicament according to the Corrected invention of case 6 exhibits synergetic antihypertensive action and antihypertensive action, and synergetic action for inhibiting arteriosclerosis by improving remodeling of the vessel.

On the other hand, it is described in Evidence A No. 3 that using the angiotensin II-receptor antagonist and calcium antagonist in combination exhibits additive or synergetic effect (Indication 3D). However, the description only teaches that using the angiotensin II-receptor antagonist and calcium antagonist in combination may exhibit additive effect or may exhibit synergetic effect, and does not teach that using olmesartan as the angiotensin II-receptor antagonist and azelnidipine as the calcium antagonist in combination exhibits synergetic effect.

In addition, it cannot be said that the above 2 kinds of synergetic effect with use

of olmesartan and azelnidipine in combination can be predicted from the description of Evidence A No. 8, A No. 9, and A No. 14 to A No. 17, even though a person skilled in the art has common general technical knowledge alleged by the demandant.

Thus, with the reasons described in "Regarding (c)" to "Regarding (f)," it cannot be said that the Corrected invention of case 6 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 8 and well-known arts if necessary, taking Evidence A No. 9 and No. 14 to No. 17 into consideration.

(2) Regarding Corrected invention of case 7
A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected invention of case 7 is as follows.
(a) The Corrected invention of case 7 is corrected so that (1) active ingredients consist of "a compound (A) (substance selected from the group consisting of olmesartan and pharmacologically acceptable esters thereof, and pharmacologically acceptable salts thereof)" and "a compound (B) (azelnidipine)," and (2) the medicament according to the Corrected invention of case 7 has action for inhibiting arteriosclerosis by inhibiting remodeling of the vessel; however, the Corrected invention of case 7 remains invalid in view of the Reasons for invalidation 1. The limitation regarding (1) is similar to that of the Corrected invention of case 6, and the limitation regarding (2) is different from that of the Corrected invention of case 6.

Regarding (1), with the same reasons as described in the paragraph regarding the Corrected invention of case 6, the Corrected invention of case 7 lacks inventive step before and after Correction.

The limitation regarding (2) is not present in the Corrected invention of case 6. Regarding the limitation, it is described in the Description of the case that remodeling of the vessels indicates "structural changes in the vessels caused by hemodynamic changes such as changes of blood flow and tension of blood vessel walls" (lines 5 to 6 on page 4). If that is the case, the medicament for prevention and/or treatment of hypertension according to the Corrected invention has "action for lowering blood pressure," and it can be said that the medicament has "action for inhibiting arteriosclerosis" by remodeling of the vessel certainly in accordance with the reduced blood pressure. Thus, the limitation regarding (2) does not limit the medicament substantially, so long as the medicament according to the Corrected invention has "action for lowering blood pressure."

Thus, the Corrected invention of case 7 has Reasons for invalidation, similar to the Corrected invention of case 6, so long as the Corrected invention of case 6 has the Reasons for invalidation.

In addition, even if "action for inhibiting arteriosclerosis" of the Corrected invention of case 7 is independent of action for lowering blood pressure, the Corrected invention of case 7 has the Reasons for invalidation.

That is, as described above, olmesartan medoxomil has been expected to be useful in treatment of atherosclerosis with an animal experiment (using crab-eating macaques with diet-induced hyperlipidemia), and it has been thought that the effect is independent of the antihypertensive action (Evidence A No. 14). Further, azelnidipine has been thought to have usefulness especially for arteriosclerosis, since the agent has higher affinity to vascular tissue and lipophilicity, compared with amlodipine which is a typical third-generation calcium antagonist and had often been formulated as of the priority date of the Patent (Evidence A No. 15 to A No. 17).

In addition, since arteriosclerosis is a disease closely associated with hypertension, it is expected to have better antihypertensive action if arteriosclerosis can be treated simultaneously.

Thus, even though the "action for inhibiting arteriosclerosis" of the Corrected invention of case 7 is independent of action for lowering blood pressure, selection of "olmesartan medoxomil" (ARB) and "azelnidipine" (CCB) having action for lowering blood pressure and action for inhibiting arteriosclerosis as the combination of ARB and CCB would have been easily made. Since "inhibiting remodeling of the vessels" is only a mechanism of inhibiting arteriosclerosis, it is obvious that this specified matter does not have effect on the determination.

In addition, it cannot be acknowledged that the effect of the Corrected invention of case 7 is a so-called "advantageous effect" similar to that of the Corrected invention of case 6.

Thus, the Corrected invention of case 7 lacks inventive step and is invalidated based on Evidence A No. 8, taking Evidence A No. 14 to A No. 17 into consideration.

B It can be said that the Corrected invention of case 7 is an invention substantially limiting the Corrected invention of case 6 by adding matters specifying the Invention of "the medicament has effect for inhibiting arteriosclerosis by inhibiting remodeling of the vessels" to the Corrected invention of case 6.

Thus, with the same reasons as for the Corrected invention of case 6, it cannot

be said that the Corrected invention of case 7 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 8 and well-known arts if necessary, taking Evidence A No. 9 and No. 14 to No. 17 into consideration.

Thus, the patent regarding the Corrected invention of case 7 cannot be invalidated based on the Reasons for invalidation 1.

(3) Regarding Corrected inventions of cases 8 to 21

A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected inventions of cases 8 to 21 is that each of the Corrected inventions of cases 8 to 21 is an invention in which the feature of the invention is not added to the Corrected invention of case 6, and the Corrected inventions of cases 8 to 21 lack inventive step because the Corrected invention of case 6 lacks inventive step.

The specific reasons are as follows.

The Corrected inventions of cases 8 to 21 are inventions specifying "disease derived from hypertension" of the Corrected invention of case 6, as "heart disease," "angina pectoris," "myocardial infarction," "arrhythmia," "sudden death," "heart failure", "cardiac hypertrophy", "a renal disease", "diabetic nephropathy", "glomerulonephritis," "nephrosclerosis," "cerebrovascular disease," "cerebral infarction," and "cerebral hemorrhage," in this order. However, the specified matter of "a medicament for the prevention and/or treatment of hypertension" lacks inventive step, as described in inventive step of patent invention 6, and thus at least this specified matter of the patent inventions 8 to 21 lacks inventive step with the same reason. Further, these specific diseases are "diseases derived from hypertension." Since it is acknowledged that the specified matter of "a medicament for the prevention and/or treatment of hypertension" lacks inventive step, the specified matter of "disease derived from hypertension" or "a medicament for the prevention and/or treatment" of any of the above specific diseases also lacks inventive step.

B The Corrected inventions of cases 8 to 21 are respectively dependent on the Corrected invention of case 6 and are also limited, and with the same reason as for the Corrected invention of case 6, it cannot be said that the Corrected inventions of cases 8 to 21 would have been easily made by a person skilled in the art based on Evidence A No. 8 and well-known arts if necessary, taking into consideration Evidence A No. 9 and No. 14 to No. 17.

Thus, the patent regarding the Corrected inventions of cases 8 to 21 cannot be invalidated based on the Reasons for invalidation 1.

(4) Regarding Corrected invention of case 22

A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected invention of case 22 is that the Corrected invention of case 22 is an invention limiting the medicament according to any of patent inventions 1 to 21 to "the compound (A) is 5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-carboxylate," with the specified matter of this compound being olmesartan medoxomil, and therefore the Corrected invention of case 22 lacks inventive step as examined in inventive step of the Corrected invention of case 6. Thus, the Corrected invention of case 22 lacks inventive step, because each of the patent inventions 6 to 21 lacks inventive step.

B The main point of the Reasons for invalidation 1 regarding the Corrected invention of case 22 is that the Corrected invention of case 22 lacks inventive step, because each of the Corrected inventions of cases 6 to 21 lacks inventive step with the Reasons for invalidation 1, and as described in above (1) to (3), the Corrected inventions of cases 6 to 21 cannot be invalidated based on the Reasons for invalidation 1.

Thus, the patent regarding the Corrected invention of case 22 cannot be invalidated based on the Reasons for invalidation 1.

(5) Regarding Corrected invention of case 23

A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected invention of case 23 is that the Corrected invention of case 23 is an invention limiting the medicament according to the Corrected inventions of cases 1 to 22 to "the medicament is a pharmaceutical composition comprising the compound (A) and the compound (B) as active ingredients," it cannot be acknowledged that the specified matter of "a pharmaceutical composition" has no feature of the invention, and the Corrected invention of the case 23 lacks inventive step because the Corrected inventions of cases 6 to 22 lack inventive step.

B The main point of the Reasons for invalidation 1 regarding the Corrected invention of case 23 is that the Corrected invention of case 23 lacks inventive step, because each of the Corrected inventions of cases 6 to 22 lacks inventive step with the Reasons for invalidation 1, and as described above in (1) to (4), the Corrected inventions of cases 6 to 22 cannot be invalidated based on the Reasons for invalidation 1.

Thus, the patent regarding the Corrected invention of case 23 cannot be

invalidated based on the Reasons for invalidation 1.

(6) Regarding Corrected invention of case 24

A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected invention of case 24 is that the Corrected invention of case 24 is an invention limiting the medicament according to the Corrected invention of case 23 to "the medicament is a physically single formulation," it cannot be acknowledged that the specified matter of "the medicament is a physically single formulation" has no feature of the invention, and the Corrected invention of case 24 lacks inventive step because the Corrected invention of case 23 lacks inventive step.

B The main point of the Reasons for invalidation 1 regarding the Corrected invention of case 24 is that the Corrected invention of case 24 lacks inventive step because the Corrected invention of case 23 lacks inventive step with the Reasons for invalidation 1, and as described above in (5), the Corrected invention of case 23 cannot be invalidated based on the Reasons for invalidation 1.

Thus, the patent regarding the Corrected invention of case 24 cannot be invalidated based on the Reasons for invalidation 1.

(7) Regarding Corrected invention of case 25

A The outline of the main point of the Reasons for invalidation 1 regarding the Corrected invention of case 25 is that the Corrected invention of case 25 is an invention limiting the medicament according to the Corrected inventions of cases 1 to 22 to "the medicament for administering a compound (A) and a compound (B) at the same time or separately at certain intervals," it can be acknowledged that the specified matter has no feature of the invention, and the Corrected invention of case 25 lacks inventive step because each of the patent inventions 6 to 22 lacks inventive step.

B The main point of the Reasons for invalidation 1 regarding the Corrected invention of case 25 is that the Corrected invention of case 25 lacks inventive step because each of the Corrected inventions of cases 6 to 22 lacks inventive step with the Reasons for invalidation 1, and as described in (1) to (4) above, the Corrected inventions of cases 6 to 22 cannot be invalidated based on the Reasons for invalidation 1.

Thus, the patent regarding the Corrected invention of case 25 cannot be invalidated based on the Reasons for invalidation 1.

6-2. Regarding Reasons for invalidation 2

A The outline of the main point of the Reasons for invalidation 2 regarding the Corrected invention of case 6 is the following (a) to (f).

(a) From the described matters of Indication 10A and 10B of Evidence A No. 10, the invention of "a hypertensive therapy comprising the step of administering olmesartan medoxomil of angiotensin II-receptor antagonist, HCTZ, and amlodipine besylate of calcium antagonist, in this order." (hereinafter referred to as the "Invention A-10") is described in Evidence A No. 10.

(b) Comparing the Corrected invention of case 6 with the invention described in Evidence A No. 10, the corresponding feature and different features are as follows.

<Corresponding feature>

Both inventions use olmesartan medoxomil of angiotensin II-receptor antagonist and calcium antagonist, as active ingredients, for treatment of hypertension.

<The different features>

1. In the case of the Corrected invention of case 6, the calcium antagonist is "azelnidipine"; on the other hand, in the invention described in Evidence A No. 10, the calcium antagonist is "amlodipine besylate."

2. The Patent invention 6 is an invention regarding "a product" (a medicament); on the other hand, the invention described in Evidence A No. 10 is "a process" (a therapy).

Whether the invention is "a product" (a medicament) or "a process" (a therapy) is a difference only in expression of categories, and is not a substantial difference.

(c) As of the priority date for the Patent, it was well-known that using an angiotensin II-receptor antagonist and a calcium antagonist in combination had possibility to exhibit excellent additive or synergetic effect (Evidence A No. 3), and on the basis of the knowledge, combinations of various angiotensin II-receptor antagonists and calcium antagonists have been used as described in Evidence A No. 4 to A No. 7.

Under such conditions, replacing the "calcium antagonist" with "azelnidipine" having a structure similar to amlodipine besylate, for the purpose of exhibiting synergetic effect, would have been easily conceived by a person skilled in the art having access to the description of Evidence A No. 10 in which the invention of using olmesartan medoxomil and amlodipine besylate in combination is disclosed.

Further, considering the descriptions of Evidence A No. 3, A No. 4, A No. 5, A No. 8, and A No. 10 that using an AII receptor antagonist (ARB) and a diuretic or calcium antagonist (CCB) in combination exhibits excellent additive or synergetic effect,

it should be regarded that diuretic and CCB are equivalent in combination with angiotensin II-receptor antagonist. The Invention A-10 is administration of olmesartan medoxomil (ARB) and amlodipine besylate (CCB), as well as hydrochlorothiazide (HCTZ), a typical diuretic, in combination, it can be regarded that HCTZ of the Invention A-10 and CCB are equivalent in the combination with ARB, and thus using olmesartan medoxomil (ARB) and amlodipine besylate (CCB) in combination can be acknowledged from the description of Evidence A No. 10. Further, since a person skilled in the art would have understand that HCTZ has been thought to have adverse effect on arteriosclerosis from the descriptions of Evidence A No. 18 and Evidence A No. 19, there is no difficulty in the Invention A-10 to replace "HCTZ" with "CCB" equivalent as the combination with ARB in a case of hypertensive therapy exhibiting anti-atherogenic action.

Thus, the Corrected invention of case 6 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 10.

(d) It is described in Evidence A No. 9 that azelnidipine as CCB and olmesartan as ARB have been applied, and accumulation of azelnidipine in the body with long-term dosing was not observed; on the other hand, accumulation in body was observed in case of amlodipine, and it is necessary to collect evidence from large clinical trials regarding ARB mainly, and to pay attention to development of purposeful combination drugs such as ARB + diuretic, and it is clear that a person skilled in the art having access to the descriptions is strongly motivated to replace "amlodipine" which was the mainstream of calcium antagonists at this time with "azelnidipine," in a combination with olmesartan, which has the same action as amlodipine without observed accumulation in the body with long-term dosing, which is the defect of amlodipine.

Further, using olmesartan medoxomil (ARB) and amlodipine besylate (CCB) in combination, other than HCTZ (diuretic), can be acknowledged from the Invention A-10 as described in (c) above.

Thus, the patent invention 6 would have been easily made by a person skilled in the art based on the invention described in Evidence A No. 10, taking Evidence A No. 9 into consideration.

(e) Replacing "amlodipine besylate" with "azelnidipine" is easy by taking Evidence A No. 15 to A No. 17 into consideration as described in "6-1. Reasons for invalidation 1(1)A(e)."

Thus, the Corrected invention of case 6 would have been easily made by a

person skilled in the art based on the invention described in Evidence A No. 10, taking Evidence A No. 9 and A No. 15 to A No. 17 into consideration.

(f) The patent invention has no so-called "advantageous effect" to be predicted or to be acknowledged as described in "6-1. Reasons for invalidation 1(a)A(f)."

B However, the body, with reasons described below, judges that the patent regarding the Corrected invention of case 6 cannot be invalidated based on Reasons for invalidation 2.

Regarding (c)

For a person skilled in the art having access to the description of Evidence A No. 10, to make the medicament according to the Corrected invention of case 6 based on the Invention A-10, the person skilled in the art firstly has to remove HCTZ from the therapy according to the Invention A-10 and examine and use amlodipine besylate and olmesartan in combination, has to think of the chemical structure of azelnidipine based on the chemical structure of amlodipine besylate and the use of azelnidipine instead of amlodipine besylate, and has to develop a production method of azelnidipine.

However, taking the description of Indication 10B of Evidence A No. 10 into consideration, the Invention A-10 is a therapy in which HCTZ is added when effect of olmesartan is not sufficiently exhibited, and amlodipine besylate is added when effect of HCTZ is not sufficiently exhibited, and HCTZ is thought to have priority over amlodipine besylate. Thus, it cannot be said that the person skilled in the art would have been able to remove HCTZ which is preferentially administered in the therapy according to the Invention A-10 and use amlodipine besylate, which is subordinated and olmesartan in combination, which is opposite the description of Evidence A No. 10, without requiring particular inventiveness, even though the person skilled in the art has common general technical knowledge alleged by the demandant.

For this reason, there is no room to examine whether replacing amlodipine besylate with azelnidipine lacks inventive step, just to be sure to examine, with the same reasons as those indicated in "Regarding (c)" of "6-1. Reasons for invalidation 1(1)B," even though the person skilled in the art has common general technical knowledge alleged by the demandant, it can be acknowledged that various steps of inventiveness and trial and error are required, and thus it cannot be said that the person skilled in the art would have been able to think of and actually implement the above idea without requiring particular inventiveness.

Taking the descriptions of Evidence A No. 3, A No. 4, A No. 5, A No. 8, and A No. 10 into consideration, it can be understood that using a diuretic or CCB and angiotensin II-receptor antagonist in combination was examined at the time of the priority date for the Patent; however, it cannot be acknowledged that a diuretic and CCB are equivalent in the combination and diuretic and CCB can be replaced with each other. Even though it was known as of the priority date of the Patent that HCTZ has adverse effect on arteriosclerosis (Indications 18A, 19A), it cannot be said that a person skilled in the art would have been able to replace HCTZ with CCB without requiring particular inventiveness. If the replacement was possible, there would be no motivation to use CCB in the Invention A-10 using CCB or to replace other CCB in the Invention A-10, and even though the person skilled in the art has common general technical knowledge alleged by the demandant, it can be acknowledged that various steps of inventiveness and trial and error are required, and thus it cannot be said that the person skilled in the art would have been able to think of and actually implement the above idea without requiring particular inventiveness.

Regarding (d)

As described in (c), it cannot be said that the person skilled in the art would have been able to remove HCTZ which is preferentially administered in the therapy according to the Invention A-10 and use amlodipine besylate which is subordinated and olmesartan in combination, which is opposite to the description of Evidence A No. 10, without requiring particular inventiveness, even though the person skilled in the art has common general technical knowledge alleged by the demandant, and there is no room to examine whether replacing amlodipine besylate with azelnidipine lacks of inventive step, just to be sure to examine, taking Indication 10B of Evidence A No. 10 into consideration; it is described that target blood pressure was achieved in patients at high level by administering olmesartan and HCTZ and further administering amlodipine besylate, and thus amlodipine besylate of the Invention A-10 is thought to be a medicament to achieve the target blood pressure. For this reason, even though the person skilled in the art has common general technical knowledge alleged by the demandant and has access to Evidence A No. 10 and Evidence A No. 9, it cannot be said that the person skilled in the art would have been able to replace amlodipine besylate, a medicament capable of achieving the target blood pressure in the Invention A-10, with azelnidipine described in Evidence A No. 9 without requiring particular inventiveness.

Regarding (e)

The indication in the above (d) is not changed even though a person skilled in the art has access to Evidence A No. 15 to A No. 17 in which it is described that olmesartan or azelnidipine has effect on arteriosclerosis.

Regarding (f)

The Corrected invention of case 6 has synergetic effect of antihypertensive action (Example 2) and action for remodeling of the vessel/ arteriosclerosis action (Example 1) as indicated in "Regarding (f)" of "6-1. Reasons for invalidation 1(1)B."

Regarding action for remodeling of the vessel, it can be understood from the drawings of Evidence B No. 13 that action of azelnidipine for reducing neointimal formation is substantially the same as that of amlodipine, and the effect is not significant at 1 mg/Kg/day (Indication B No. 13A). On the other hand, in a case of using azelnidipine or amlodipine, and olmesartan in combination, it can be acknowledged that a group administered azelnidipine and olmesartan in combination had significantly excellent action compared with a group administered amlodipine and olmesartan in combination (Indications B No. 3A and B No. 3 B).

In addition, it cannot be said that a person skilled in the art can predict the effect in a case of using azelnidipine and olmesartan in combination of exhibiting synergetic effect of the above two actions and has significantly excellent action as compared with a case of using amlodipine and olmesartan in combination, from the descriptions of Evidence A No. 10, A No. 9, and A No. 15 to A No. 17, even though the person skilled in the art has common general technical knowledge alleged by the demandant.

Thus, with the reasons described in (c) to (f) above, it cannot be said that the Corrected invention of case 6 would have been easily made by a person skilled in the art based on Evidence A No. 10, and well-known arts if necessary, taking into consideration Evidence A No. 9 and No. 15 to No. 17.

(2) Regarding corrected invention of case 7

A The outline of the main point of Reasons for invalidation 2 regarding corrected invention of case 7 is as follows.

The limitations of (1) and (2) above regarding the Corrected invention of case 7 do not affect judgment of inventive step as described in "Regarding (A)" of "6-1. Reasons for invalidation 1(2)," and thus the Corrected invention of case 7 has the Reasons for invalidation 2 as long as the Corrected invention of case 6 has the Reasons

for invalidation 2.

Further, even though the "action for inhibiting arteriosclerosis" of the Corrected invention of case 7 is independent of the action for lowering blood pressure, the conclusion is not changed as described in "Regarding (A)" of "6-1. Reasons for invalidation 1(2)." That is, the Corrected invention of case 7 lacks inventive step and should be invalidated based on Evidence A No. 10, taking Evidence A No. 15 to A No. 17 into consideration.

B It can be said that the Corrected invention of case 7 is an invention substantially limiting the Corrected invention of case 6 by adding the matters specifying the Invention of "and the medicament has effect of inhibiting remodeling of the vessels" to the Corrected invention of case 6.

With the same reasons as the Corrected invention of case 6, it cannot be said that the Corrected invention of case 7 would have been easily made by a person skilled in the art based on Evidence A No. 10, and well-known arts if necessary, taking into consideration Evidence A No. 9 and No. 15 to No. 17.

Thus, the patent according to the Corrected invention of case 7 cannot be invalidated based on the Reasons for invalidation 2.

(3) Regarding corrected inventions of cases 8 to 25

A The outline of the main point of Reasons for invalidation 2 regarding the Corrected inventions of cases 8 to 25 is that since the Corrected inventions of cases 8 to 25 are dependent on the Corrected invention of case 6 or 7, the Corrected inventions of cases 8 to 25 have no feature of the invention with respect to the Corrected invention of case 6 or 7, and the patent inventions 6 and 7 lack inventive step as examined in (1) and (2) above, the Corrected inventions of cases 8 to 25 have the same reasons for invalidation as the Corrected invention of case 6 or 7.

B The main point of Reasons for invalidation 2 regarding the Corrected inventions of cases 8 to 25 is that since the Corrected inventions of cases 6 and 7 lack inventive step with the Reasons for invalidation 2, the Corrected inventions of cases 8 to 25 also lack inventive step; on the other hand, Reasons for invalidation 2 cannot invalidate the Corrected inventions of cases 6 and 7 as described above in (1) and (2).

Thus, the Reasons for invalidation 2 cannot invalidate the Corrected inventions 8 to 25 of the case.

Evidence A No. 1 and A No. 2 which were submitted with written demand for trial show the structure and effect of compounds (A) and (B) of the Corrected invention, however, are publications distributed after the priority date for the Patent. Evidence A No. 20 and A No. 21 which were submitted with an oral proceedings statement brief show that olmesartan medoxomil and azelnidipine were known as of the priority date of the Patent, Evidence A No. 3-1 indicates that the description of Evidence A No. 3 is objective and indicates state of the art as of the priority date of the Patent, Evidence A No. 6-1 is a partial translation of Evidence A No. 6, Evidence A No. 14-1 is a partial translation of Evidence A No. 14, and Evidence A No. 14-2 indicates the day on which Evidence A No. 14 was distributed, and thus the descriptions of evidences A do not affect the above acknowledgment and judgment.

6-3. Closing

Therefore, the patent regarding the Corrected inventions of cases 6 to 25 cannot be invalidated based on the Reasons for invalidation 1 and 2.

7. Closing

As described above, request for correction of the case shall be approved, and it cannot be said that the patent regarding the Corrected inventions of cases 6 to 25 should be invalidated based on the Reasons for invalidation 1 and 2.

The costs in connection with the trial shall be borne by the demandant under the provisions of Article 61 of the Code of Civil Procedure which is applied mutatis mutandis in the provisions of Article 169(2) of the Patent Act.

Therefore, the trial decision shall be made as described in the conclusion.

March 10, 2017

Chief administrative judge: NAITO, Shinichi
Administrative judge: ANABUKI, Satoko
Administrative judge: MATSUZAWA, Yuko