Trial Decision

Invalidation No. 2007-800192

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Regarding the patent invalidation trial case of the above-mentioned patent No. 3546058 of the invention "Use of carbazole compounds for the treatment of congestive heart failure" between the parties above, the trial decision is made as follows:

Conclusion

The correction shall be approved.

The patent regarding the inventions according to Claims 1 to 10 of Japanese Patent No. 3546058 was invalidated.

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

Reasons

1. History of the procedures

The present application for the inventions according to claims 1 to 10 of the present patent No. 3546058 was filed on February 7, 1996 (Priority claim under the Paris Convention: February 8, 1995, Germany; June 7, 1995, USA) as an international filing date by Boehringer Mannheim Pharmaceuticals Corporation-Smithkline Beecham Corporation Limited Partnership #1.

Then, the establishment of the patent right was registered on April 16, 2004. Subsequently, after the registration of the request for trial, the registered holder was changed to Boehringer Mannheim Pharmaceuticals Corporation-Smithkline Beckman Corporation Limited Partnership #1 on September, 17, 2008. Furthermore, on the same date, the registration was transferred to Roche Therapeutics Incorporated F. Hoffmann-La Roche Aktiengesellschaft and further, on the same date, transferred to the demandee Daichi Sankyo Co., Ltd. Thus, Daichi Sankyo Co., Ltd. takes over the proceedings of this case.

Against this, the demandant Sawai Pharmaceutical Co., Ltd. demanded trial for patent invalidation of all the claims on September 13, 2007. Furthermore, on March 3, 2008, the demandee submitted a written correction request together with a written statement to request for correction.

The first oral proceeding was conducted on August 27, 2008. The demandant filed an oral proceedings statement brief on August 19, 2008 prior to the first oral proceeding, while the demandee filed an oral proceedings statement brief on August 14, 2008.

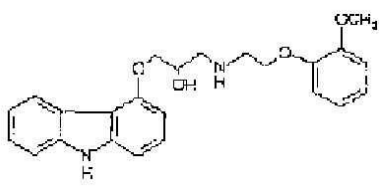
Subsequently, the demandant filed a written statement on September 22, 2008, while the demandee filed written statements on September 19 and October 27, 2008, respectively.

2. Request for correction

(1) Contents of correction

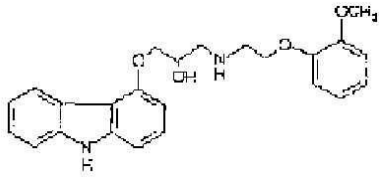
(Correction A)

Claim 1 before correction, which is read as
"[Claim 1] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals, alone or in conjunction with one or more of other pharmaceutical agents, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist:



wherein the pharmaceutical agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides." is corrected so as to read as follows and is provided as new claim 1:

"[Claim 1] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin, alone or in conjunction with one or more of other pharmaceutical agents, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist:



wherein the pharmaceutical agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides."

Since claims 2 to 7 and 10 of the scope of claims in the corrected specification are dependent on claim 1, these claims are corrected in a manner similar to the correction of claim 1 even though they are not mentioned in Correction A stated above.

(Correction B)

Claim 8 before correction, which is read as

"[Claim 8] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals according to the regimen of:

(a) administrating a pharmaceutical formulation that contains 3.125-mg or 6.25-mg carvedilol per single unit for a period of 7 to 28 days, once or twice daily;

(b) subsequently administrating a pharmaceutical formulation that contains 12.5-mg carvedilol per single unit for an additional period of 7 to 28 days, once or twice daily; and

(c) finally administrating a pharmaceutical formulation that contains 25.0-mg or 50.0-mg carvedilol per single unit, once or twice daily as a maintenance dosage." is corrected so as to read as follows and is provided as new claim 8:

"[Claim 8] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin according to the regimen of:

(a) administrating a pharmaceutical formulation that contains 3.125-mg or 6.25-mg carvedilol per single unit for a period of 7 to 28 days, once or twice daily;

(b) subsequently administrating a pharmaceutical formulation that contains 12.5-mg carvedilol per single unit for an additional period of 7 to 28 days, once or twice daily; and

(c) finally administrating a pharmaceutical formulation that contains 25.0-mg or 50.0-mg carvedilol per single unit, once or twice daily as a maintenance dosage."

Since claim 9 of the scope of claims in the corrected specification is dependent on claim 8, claim 9 is corrected in a manner similar to the correction of claim 8 even

though it is not mentioned in Correction B stated above.

(2) The suitability of the purpose of correction, the presence or absence of new matters, and the extension or change of scope of claims

Corrections A and B correct "mammals" stated in Claims 1 and 8 before correction to "mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin," respectively.

The correction confines the subjects to which pharmaceutical agents are administered from "mammals" before correction to "mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin" after correction. Thus, both Corrections A and B intend to restrict the scope of claims.

"EXPERIMENTAL" in the Detailed Description of the Invention in the present specification, which describes specific examples of administration of carvedilol to patients, states that targets of the administration are patients on background therapy with diuretics, ACE inhibitors, and/or digoxin" (the present Japanese patent publication, page 7, lines 32 to 33). Thus, Corrections A and B are within the scope of the matters described in the description and other materials of the patent and do not substantially enlarge or modify the scope of claims of the patent.

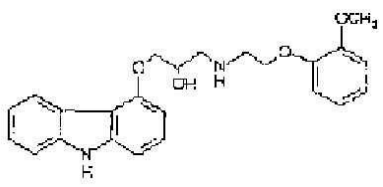
(3) Summary

A described above, each of the request of correction for claims 1 to 7 and 10 (Correction A) and the request of correction for claims 8 and 9 (Correction B) falls under the provisions of Article 126(3) and (4) of the Patent Act, which is applied mutatis mutandis pursuant to Article 134-2(1) and (5) of the Patent Act. Corrections A and B are therefore approved.

3. The Invention

Since the correction was approved as described above, the inventions according to claims 1 to 10 of the present patent No. 3546058 are specified by the matters stated in claims 1 to 10 of the scope of claims in the corrected specification attached to the written correction request and are read as follows:

[Claim 1] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin, alone or in conjunction with one or more of other pharmaceutical agents, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist:



wherein the pharmaceutical agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides.

[Claim 2] The use of carvedilol as described in claim 1, wherein the use comprises administering a pharmaceutical formulation as first dosages once or twice daily, for a period of from 7 to 28 days, said first dosages each comprising carvedilol in an amount of 3.125 mg or 6.25 mg in a single unit.

[Claim 3] The use of carvedilol e as described in claim 1, wherein the use comprises administering a pharmaceutical formulation once or twice daily, for a period of from 7 to 28 days, said pharmaceutical formulation comprising carvedilol in an amount of 12.5 mg in a single unit.

[Claim 4] The use of carvedilol as described in claim 1, wherein the use comprises administering a pharmaceutical formulation as t maintenance dosages once or twice daily, said maintenance dosages each comprising carvedilol in an amount of 25.0 mg or 50.0 mg in a single unit.

[Claim 5] The use of carvedilol e as described in claim 1, wherein the angiotensin converting enzyme is selected from the group consisting of captopril, lisinopril, fosinopril, and enalapril, and any pharmaceutically acceptable salts thereof.

[Claim 6] The use of carvedilol as described in claim 1, wherein the diuretic is selected from the group consisting of hydrochlorothiazide, torasemide, furosemide, and any pharmaceutically acceptable salts thereof.

[Claim 7] The use of carvedilol as described in claim 1, wherein the cardiac glycoside is selected from the group consisting of digoxin, β-methyl-digoxin, and digitoxin.

[Claim 8] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin according to the regimen of:

(a) administrating a pharmaceutical formulation that contains 3.125-mg or 6.25-mg carvedilol per single unit for a period of 7 to 28 days, once or twice daily;

(b) subsequently administrating a pharmaceutical formulation that contains 12.5-mg carvedilol per single unit for an additional period of 7 to 28 days, once or twice daily; and

(c) finally administrating a pharmaceutical formulation that contains 25.0-mg or 50.0-mg carvedilol per single unit, once or twice daily as a maintenance dosage.

[Claim 9] The use of carvedilol according to claim 8, wherein the use comprises administration of carvedilol alone or in combination with one or more of other pharmaceutical agents, and the pharmaceutical agent is selected from angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides.

[Claim 10] The use of carvedilol according to claim 1, wherein carvedilol is used for the preparation of a medicament for treating congestive heart failure and the medicament can be administered at a daily maintenance dosage of 10 to 100-mg carvedilol, the medicament being administered following an incremental dosing scheme including a three-stage administration regimen, the scheme comprising:

a first regimen in which 10 to 30% of the daily maintenance dosage of carvedilol is administered for a period of 7 to 28 days;

a second regimen in which 20 to 70% of the daily maintenance dosage of carvedilol is administered for a period of 7 to 28 days; and

a third regimen in which 100% of the daily maintenance dosage of carvedilol is administered, the third regime being initiated after the end of the second regimen.

Hereinafter, the inventions of the respective claims are individually referred to as "Invention 1," "Invention 2," ... , and "Invention 10." In addition, Inventions 1 to 10 are collectively referred to as "the Invention."

4. Overview of the party's allegation

4-1. Outline of the demandant's allegation

The demandant demands the decision "The patent for the inventions of claims 1 to 10 of Patent No. 3546058 shall be invalidated. The costs in connection with the trial shall be borne by the demandee," and submitted the following documentary evidence as a means of proof. The patent of the case should therefore be invalidated under the provisions of Article 123(1)(iv) of the Patent Act (Reasons A and B) and also should be invalidated under the provisions of Article 123(1)(ii) of the Patent Act (Reasons C and D)."

The outline of Reasons A to D is as follows:

Reason A: The inventions of the respective claims 1 to 8 and 10 of the Patent are not described in the detailed description of the invention and thus none of them corresponds to the invention for which a patent is sought. The Patent has therefore been granted on a patent application not complying with the requirements prescribed in Article 36(6)(i) and falls under Article 123(1)(iv). Thus, the Patent has been issued on a patent application that does not meet the requirements prescribed in Article 36(6)(i) of the Patent Act, and falls under Article 123(1)(iv) of the Patent Act. The Patent should therefore be invalidated.

Reason B: Each of claims 1 to 10 of the Patent is unclear as to which of three invention categories defined by the Patent Act (Article 2(3) of the Patent Act) it belongs. Thus, the Patent has been issued on a patent application that does not meet the requirements prescribed in Article 36(6)(i) of the Patent Act, and falls under Article 123(1)(iv) of the Patent Act. The Patent should therefore be invalidated.

Reason C: If it is interpreted that the category of the Invention is the invention of process, the Invention (all claims) is an invention corresponding to a method for therapy or treatment of human diseases. Thus, the Invention does not correspond to "an invention that is industrially applicable" under the provisions of Article 29(i) of the Patent Act. The Patent falls under Article 123(1)(ii) of the Patent Act and should therefore be invalidated.

Reason D: The inventions of claims 1 to 10 of the Patent are substantially identical to the inventions described in Exhibits A1 and A2 and thus lack novelty. In addition, they could be easily made by a person skilled in the art based on Exhibit A1 or A2 or based on the invention described in at least one of Exhibits A1 to A6 and thus lack inventive step. They have reasons for invalidation under the provisions of Article 29(1) and (2)

of the Patent Act. The Patent falls under Article 123(1)(ii) of the Patent Act and should therefore be invalidated.

(Means of proof)
Exhibit A1: Journal of Cardiovascular Pharmacology 19 (suppl.1): S62−S67, 1992
Exhibit A2: J. Am. Coll. Cardiol. vol. 24. No. 7 December 1994; 1678−1687
Exhibit A3: Postgraduate Medicine, 1994, vol. 96, No. 5, October, 167−172
Exhibit A4: Modern Medicine of Australia, 1994, February 14−24
Exhibit A5: J. Am. Coll. Cardiol. vol. 22. No. 4 October 1993; 194A−197A
Exhibit A6: Drug Safety, 1994, 11(2), 86-93
Exhibit A7: Today's Therapy Edition 1993
Exhibit A8: Today's Therapy Edition 1994
Exhibit A9: "Heart Failure - Recent Progress" in Cardiac Practice 1990
Exhibit A10: "Heart Failure and β-Receptor" in Cardiac Practice 1990
Exhibit A11: "Prognosis of Heart Failure Patients" in Cardiac Practice 1990
Exhibit A12: The Merck Index 14th Edition 2006
(Reference materials submitted by Demandant)
1. "Introduction to Statistics in Medical Research", page 106, Table 7
2. "Clinical Trials 2003", page 19
3. IFPMA Clinical Trial Portal HP

4-2. Outline of the demandee's allegation

The demandee requested the trial decision, "The demand for trial of the case was groundless. The costs in connection with the trial shall be borne by the demandant," alleges that none of Reasons A to D for invalidation alleged by the above demandant has reasons, and filed the following matters as means of evidence.
In particular, the demandee made the following argument against Reason D.

(1) As a purpose of treating congestive heart failure at the time of the priority date of the Patent, there was a difference between the concept of improving hemodynamics and exercise capacity and the concept of improving life prognosis (improvement of mortality rate). In other words, both are distinguished in terms of pharmaceutical use. Moreover, it has not been proved that there is a correlation between the two. Improvement of the mortality rate could not be predicted from the effects of improving hemodynamics and exercise capacity of carvedilol.
(2) Even if "for decreasing mortality" is included in the concept of "treatment of congestive heart failure" at the time of the priority date, it should be permitted as a selection invention equivalent to a subordinate concept.
(3) The Invention of the Patent states a novel administration form "continuous administration for 6 months or longer" and, in this respect, differs from the statements of Exhibits A1 and 2.
(4) The mortality improvement effect of carvedilol is quite remarkable and far beyond expectation.

(Means of proof)

Exhibit B1: Lancet Vol. 362 July 5, 2003; 7-13
Exhibit B2: Am J Cardiol Vol. 71, 1993; 23C-29C
Exhibit B3: Lancet Vol. 342, December 11, 1993; 1441-1446
Exhibit B4: Circulation Vol. 90, No. 4 October, 1994; 1765-1773
Exhibit B5: Lancet Vol. 336 July 7, 1990; 1-6
Exhibit B6: EBM REPORT Heart Failure, published June 30, 2005, No. 8, published by Life Science Publishing Co. Ltd.: 16-17
Exhibit B7: Circulation Vol. 103, No. 10 March 13, 2001; 1428-1433
Exhibit B8: Am. heart J. Vol. 142, No. 3, 2001; 489-501
Exhibit B9: N Engl J Med Vol. 344 No. 22 May 31, 2001; 1659-1667
Exhibit B10: Journal of the American College of Cardiology Vol. 49 No. 9 March 6, 2007; 963-971
Exhibit B11: European Journal of Heart Failure Vol. 9, 2007; 1128-1135
Exhibit B12: Today's Therapy 1992 (Volume 34), p. 314-316, published February 15, 1992
Exhibit B13: Today's Therapy 1995 (Volume 37), p. 318-320, published February 15, 1995
Exhibit B14: Today's Therapy 1996 (Volume 38), p. 333-334, published January 1, 1996
Exhibit B15: Today's Therapy 2008, p.288-293, published January 1, 2008
Exhibit B16: Today's Therapy 1993 (Volume 35), p. 314-317, February 15, 1993
Exhibit B17: Today's Therapy 1994 (Volume 36), p. 312-313, February 15, 1994

(Reference material submitted by the demandee)
1. The written opinion dated March 10, 2003 (submitted by the applicant at the examination stage of the patent application)

5. Judgment by the body

5-1. Reason A (allegation under Article 36(6)(i) of the Patent Act)

In the statement in the scope of claims before correction, Claim 1 states "Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals ... alone or in conjunction with one or more of other pharmaceutical agents." Similarly, in the statements of claims 1 to 8 and 10, a mode in which carvedilol is administered alone can also be interpreted as being included in the inventions of the respective claims. In contrast, no statement of such an administration of carvedilol alone is found in the detailed description of the invention in the specification.

However, as stated in the above 2, the request for correction of the case should be approved. With such correction, claims 1 to 8 and 10 include the statement of "use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin ... alone or in conjunction with one or more of other pharmaceutical agents." It is therefore clear that there is no mode in which carvedilol is administered alone in the inventions of the respective claims. Thus, the inconsistency as stated above has been resolved.

Even if the word "alone" in the patent specification after correction is interpreted as "carvedilol alone to a patient undergoing therapy with other pharmaceutical agents," there is no inconsistency.

Thus, it cannot be said that the description of the patent specification does not meet the provisions of Article 36(6)(i) of the Patent Act.

5-2 Reason B (allegation under Article 36(6)(ii) of the Patent Act)

Claim 1 states "use of carvedilol in manufacture of a pharmaceutical agent ... alone or in conjunction with one or more of other pharmaceutical agent." Even if it is supposed to combine carvedilol and another pharmaceutical agent, there is no inconsistency in interpreting the statement of claim 1 as "use of carvedilol " for the manufacture of such a pharmaceutical agent because, for example, it is common practice to make a single agent containing multiple active ingredients or a plurality of separate agents in the form of a single package.

The invention of claim 1 is "a method of using a product (carvedilol) for producing a medicament"; that is, "invention of process." Thus, the category of the invention is clear and thus the statement of claim 1 cannot be said to violate the provisions of Article 36(6)(ii) of the Patent Act.

The same is also applied to any of claims 2 to 10.

5-3. Reason C (allegation with respect to the main paragraph of Article 29(1) of the Patent Act)

As stated in 5-2, the invention of each of claims 1 to 10 is recognized as "a method of using a product (carvedilol) for producing a medicament" and is evidently not an invention corresponding to a method of therapy of humans but "an invention that is industrially applicable."

Thus, the Invention cannot be recognized as one that violates the main paragraph of Article 29(1) main paragraph of the Patent Act.

5-4. Reason D (allegation under Article 29(1)(iii) and (2))

5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent

Prior to judging the novelty and inventive step of the Patent Invention, first of all, we will examine what kind of matter was common as general knowledge as of the date of the Priority Claim (hereinafter referred to as "the priority date for the Invention").

Each evidence of Exhibits A7 to A11 relates to the publications issued before the date of the Priority Claim of the Patent. Among them, Exhibits A7 and A8 are annual publications entitled "Today's Therapy." In both the publications, the foreword states that "Now 'Today's Therapy' has become a fundamental publication indispensable for clinical practice" (Exhibit A7, page 5, lines 4 to 5), "the concept of this book is ... to be able to find out the latest concrete therapeutic guidelines immediately" (Exhibit A 7, page 5, lines 10 to 11), and "Today's Therapy is the one that has been compiled intentionally with the intention to be physically accessible at the place of daily practice

and can be used immediately, be provided with content in accordance with the actual situation, and organize and briefly describe necessary information and always in the latest version" (Exhibit A 8, page 5, lines 10 to 14). In other words, "Today's Therapy" contains the latest treatment guidelines and is used in actual treatment and clinical practice. Exhibits A9 to A11 are review articles that cite a number of papers. In view of the nature of each of these evidences, it is understood that it is possible to inquire the common general technical knowledge of a person skilled in the art as of the priority date for the Invention. Considering the description of each of these evidences, therefore, we will identify what matters existed as common general technical knowledge of a person skilled in the art as of the date of the Priority Claim of the Patent.

(A) Purpose of treating congestive heart failure

For the purpose of treating congestive heart failure, Exhibits A8, A9, and A11 include the following statements:

*Exhibit A8

(8a) (Exhibit A8, page 312, right column, lines 5 to 10)

"1. Principles of heart failure treatment

Recently, in a conceptual category, heart failure is widely accepted as cardiac dysfunction accompanied by: (1) a decrease in exercise tolerability, (2) frequent occurrence of arrhythmia, and (3) a decrease in survival rate. Treatment of heart failure is aimed at (1) improving the symptoms of patients and improving the quality of life, and (2) improving the prognosis of life."

*Exhibit A9

(9a) (Exhibit A9, page 17, right column, from the bottom, lines 8 to 5)

"The first purpose of treating heart failure is to expand the range of activities and improve the quality of life, and the second is to improve the prognosis."

*Exhibit A11

(11a) (Exhibit A11, page 51, middle paragraph)

"Heart failure is a symptomatic name and not a disease name. Thus, there are many objections as to how to define it for the greatest clinical convenience. ... Cohn advocated the concept as a more useful and current definition such that cardiac dysfunction is associated with (1) decrease in exercise tolerability, (2) frequent occurrence of ventricular arrhythmia, and (3) a decrease in survival.

Based on this definition, the purpose of treating heart failure will ultimately increase the survival rate of the patient."

(11b) (Exhibit A11, page 55, right column, from the bottom, lines 10 to 9)

"After all, the ultimate goal of heart failure therapy is to increase the survival rate."

From the statements of these Exhibits A 8, 9 and 11, it can be understood that "with respect to a purpose of treating congestive heart failure, two different concepts:

(i) an improvement in life quality: and

(ii) an improvement in prognosis of life; i.e., an improvement in survival rate,

were recognized as two important goals" by a person skilled in the art as of the priority

date for the Invention.

(B) Indicators that affect the mortality rate of patients with congestive heart failure
Exhibits A9 and A11 include statements about the indicators that affect the mortality rate of patients with congestive heart failure.

*Exhibit A9
(9b) (Exhibit A9, page 18, right column, lines 7 to 8)
"The death rate is higher as the left ventricular ejection fraction decreases"
(9c) (Exhibit A9, page 18, right column, lines 16 to 18)
"In order to improve the prognosis of heart failure, it is important to prevent reduction in the contractility of myocardium and make it better if possible."
*Exhibit A11
(11c) (Exhibit A11, page 52, left column, lines 7 to 19)
"In 63 patients with dilated cardiomyopathy ..., in evaluating prognosis, Schwartz and colleagues examined the degree of significance of the morphological findings and left ventricular hemodynamic index. During the observation period of 1124 days on average, 23 patients died. In patients with ejection fraction of 35.5% or more, the cumulative survival rates are 97% in the first year, 94% in the second year, and 85% in the fourth year. On the other hand, in patients with ejection fraction less than 35.5%, the cumulative survival rates are 71%, 44%, and 41%, respectively. According to multivariate analysis, this ejection fraction is said to enable prediction of survival rate with a significant difference of $p < 0.00001$."
(11d) (Exhibit A11, page 52, left column, from the bottom, lines 10 to 3)
"Likoff and colleagues followed up 201 patients with dilated cardiomyopathy and ischemic cardiomyopathy for 28 months to examine factors that influence the mortality rate of heart failure patients. During this time, 85 deaths were observed, 31% of which were sudden death. In this case as well, the survival rate was shown to be significantly different in patients with an ejection fraction of 20% or more."
(11e) (Exhibit A11, page 52, left column, line 2 from the bottom to page 52, middle column, line 21)
"Cohn et al. reanalyzed famous trials, which revealed that the vasodilator called V-HeFT altered the survival rate of patients with chronic heart failure, to examine various factors that affect prognosis. ... The average ejection fraction of all patients at the start of the trial was 28%. The patients were then divided into a group with values greater than 28% and a group with values equal to or less than 28%. The mortality rate was significantly higher in the group with lower ejection fraction."
(11f) (Exhibit A11, page 54, right column, from the bottom, lines 10 to 4)
"The ultimate goal of heart failure therapy is to increase the survival rate of patients. Factors that deteriorate the prognosis include leading disease, left ventricular dysfunction, decrease in exercise tolerability, blood catecholamines, arrhythmia, and the like. In order to start treatment, there is a need to gain sufficient insight into prognosis for the treatment."

From the description of these Exhibits A9 and A11, it can be understood that, as of the priority date for the Invention, "with regard to patients with congestive heart failure, a person skilled in the art could have recognized that the indicators, such as the

contractility of the myocardium, and the left ventricular ejection fraction, influence the survival rate of the patients."

(C) Use of β-blockers in the treatment of congestive heart failure and the administration period thereof

Exhibits A 7, 8, and 10 include the following statements with respect to the use of β-blockers in the treatment of congestive heart failure and the administration period thereof.

*Exhibit A7
(7a) (Exhibit A7, page 316, right column, from the bottom, lines 14 to 5)

"β-blockers: Administered in a case in which there is no functional improvement attained by the treatment with the medicine and normal antiarrhythmic drugs are not effective. Cardiac functions may deteriorate temporarily. It takes several months to develop the effect.
Prescription example

Metoprolol (Ropressol): Dosing started at 5 mg/day. Observe changes in the clinical conditions of patients for about 2 months. The dose is gradually increased unless cardiac function deterioration is found. The dosing continues at 40 mg/day. There is no established regimen for congestive heart failure. Carefully select cases and increase doses."
*Exhibit A8
(8b) (Exhibit A8, page 313, left column, lines 7 to 10)

"e. β-blockers: In recent years, β-blocker therapy for dilated cardiomyopathy, which is important as an etiology of refractory heart failure, attracts attention and its effectiveness is being confirmed. Future development is therefore expected."
(8c) (Exhibit A, page 313, right column, lines 4 to 9)

"β-blocker therapy for cardiac failure due to dilated cardiomyopathy starts with a small amount and gradually increases. Long-term administration is required until the effect is developed."
11) Ropressol: a daily dose of 5 mg, which is administered in two divided doses per day. In severe cases, 2.5 mg is taken as the initial dose and dose is incremented by 5 to 10 mg at 1- to 2-week intervals, and 40 to 80 mg as maintenance dosages."
*Exhibit A10
(10a) (Exhibit A10, page 26, right column, line 4 from the bottom to page 27, left column, line 5 from the bottom)

"1. Confirmation of β-blocker administration for cardiac failure

From 1975 to 1980, the Swedish group of Waagstein, Swedberg, et al. published a paradoxical series of reports in which patients with severe dilated cardiomyopathy were chronically administered sympathetic β-receptor blockers contraindicated in cardiac failure, resulting in improvements in motor capacity, cardiac function, and life prognosis. After that, several groups conducted replication studies and confirmed that, in at least some patients with dilated cardiomyopathy, clinical improvement due to chronical administration of β-receptor blockers was confirmed by long-term administration of β-blocker by additional test. β-blocker therapy has therefore been regarded as one of the leading treatments for chronic cardiac failure including dilated cardiomyopathy."

(10b) (Exhibit A10, page 27, left column, line 4 from the bottom to page 27, middle column, the last line)

"Table 1 shows a list of reports stating that β-blockers were effective. On the other hand, Table 2 summarizes reports stating that β-blockers were not effective. When comparing the two, the reports of non-effectiveness were of short-term administration with a single dose or at most one month. On the other hand, the reports of effectiveness were of long-term administration for mostly several months or more. In many protocols, dose escalation of the drug is often increased to a maintenance dosage of 25 to 100 mg/day. In these reports stating administration for 3 months or more, improvements in subjective symptoms and exercise ability as well as improvements in cardiac functions, such as the left ventricular ejection fraction, left ventricular inner diameter, and cardiac output, were almost always recognized. Long-term administration for more than several months may therefore be necessary for the development of long-term effect. In addition, an improvement in prognosis of life was observed in a report on administering on a year-by-year basis. However, it was a study in a small number of cases and there is still room for further study for improving life prognosis."

(10c) (Exhibit A10, page 28)

表１　β遮断薬の有効例の報告

報　告　者	患者数	投与期間	薬剤・投与量	発　表　誌
スウェーデン				
①Waagstein	7	2～12ヵ月	Practolol	Brit.Heart J. **37**:1022(1975)
②Swedberg	28	2～26ヵ月	Metoprolol (50～200mg/日)	Brit.Heart J. **44**:117(1980)
③Swedberg	15	1～4ヵ月 (βブロッカー中止)	Metoprolol Alprenolol Practolol Propranolol	Brit.Heart J. **37**:134(1980)
④Waagstein	23	平均19ヵ月	Metoprolol (25～100mg/日)	JACC **5**:441(1985)
アメリカ				
⑤Weber	2	数ヵ月	Propranolol (40～80mg/日)	Am.Heart J. **104**:877(1982)
⑥Fowler	15	平均14ヵ月	Metoprolol Propranolol 平均90mg/日	JACC **3**:544(1984)
⑦Ergelmeier	32	12ヵ月	Metoprolol (6.25～100mg/日)	Circulation **72**:536(1985)
⑧Gilbert	16	3ヵ月	Bucindolol (200mg/日)	Circulation **76**:IV-358(1987)
その他				
⑨The German and Austrian xamoterol study group	220	3ヵ月	Xamoterol (200mg/日)	Lancet I:489(1988)

表２　β遮断薬の無効・悪化例の報告

報　告　者	患者数	投与期間	薬剤・投与量	発　表　誌
イギリス				
① Ikram	10	単回投与	Acebutolol 10mg iv	Brit.Heart J. **42**:311(1979)
② Ikram	15	単回投与	Acebutolol 40mg	Lancet I:490(1981)
③ Taylor	8	単回投与	Oxprenolol 20mg	Lancet II:835(1981)
④ Currie	10	単回投与	Metoprolol 100～200mg	JACC **3**:203(1984)
その他				
⑤ Hoffbrand	1	単回投与	Propranolol 10mg	Lancet(letter) I:1031(1980)
⑥ Brezis	2	2日 単回投与	Propranolol 80mg, 20mg	Am.Heart J.(letter) **101**:357(1981)
⑦ Binkley	10	単回投与	Pindolol 5mg	Circulation **74**:1390(1986)
⑧ Shanes	30	単回投与	Pindolol(01.～0.4mg iv) Propranolol(1～4mg iv)	Am.Heart J. **116**:1268(1988)

表１　β遮断薬の有効例の報告　　Table 1 Report on Effective Examples of β-Blocker

報告者 Reporter
患者数 Number of patients
投与期間 Administration period
薬剤・投与量 Drug/dose
発表誌 Published journal
スウェーデン Sweden
アメリカ U.S.A
その他 Others
２～１２ヵ月 2 to 12 months
２～２６ヵ月 2 to 26 months
１～４ヵ月 1 to 4 months
βブロッカー中止 Canceled β-blocker
平均１９ヵ月 19 months on average
数ヵ月 Several months
平均１４ヵ月 14 months on average
１２ヵ月 Twelve months
３ヵ月 Three months
日 Day

表２ β遮断薬の無効・悪化例の報告 Table 2 Report of cases of ineffectiveness/deterioration of β-blockers
イギリス UK
単回投与 Single dose
２日 2 days

(10d) (Exhibit A10, page 31, left column, lines 1 to 16)

"Selection and introduction of β-blockers

In order to reduce the risk of circulation failure at the time of introduction, it is important to start from a smaller dose and gradually increase the dose. Increasing the dose should be carefully performed in severe cases in which sympathetic nervous activity is accelerated remarkably. ... In the most reported metoprolol, it starts at 5 to 20 mg/day depending on the severity and is increased by the same amount every 1 to 2 weeks. Ultimately the patient is often able to withstand the usual dose (40 to 80 mg/day in metoprolol)."

From the statements in Exhibits A 7, 8, and 10, it can be understood that "β-blockers were previously contraindicated for cardiac failure and the usefulness of β-blockers was not established in clinical practice. In addition, ineffectiveness/deterioration cases had been reported at the same time. Under such circumstances, numerous reports in which cases were considered effective as a result of deliberate and long-term administration, depending on at least the circumstances of patients, had been received. On the premise that care should start with a small dose at the start of administration, β-blockers were recognized as one of the leading

pharmaceutical agents of congestive heart failure."

It can be understood that a person skilled in the art could recognize that "it takes more than a few months to develop the effects of β-blockers" and "although there was a report that prognosis was improved by yearly administration, it had not been conclusively recognized by a person skilled in the art."

Based on the common general technical knowledge as of the priority date for the Invention; i.e., based on the following items (A) to (C-3), Reason D for the Invention will be examined below.

(A) "With respect to a purpose of treating congestive heart failure, two different concepts:

(i) an improvement in life quality: and

(ii) an improvement in prognosis of life; i.e., an improvement in survival rate,

were recognized as two important goals."

(B) "With regard to patients with congestive heart failure, a person skilled in the art could have recognized that certain indicators, such as the contractility of the myocardium, and the left ventricular ejection fraction, influence the survival rate of the patients."

(C-1) "β-blockers were previously contraindicated for cardiac failure and the usefulness of β-blockers was not established in clinical practice. In addition, ineffectiveness/deterioration cases had been reported at the same time. Under such circumstances, numerous reports in which cases were considered effective as a result of deliberate and long-term administration, depending on at least the circumstances of patients, had been received. On the premise that care should start with a small dose at the start of administration, β-blockers were recognized as one of the leading pharmaceutical agents of congestive heart failure."

(C-2) "It takes more than a few months to develop the effects of β-blockers."

(C-3) "Although there was a report that prognosis was improved by yearly administration, it had not been conclusively recognized by a person skilled in the art."

5-4-2. Regarding Invention 1 (Invention of claim 1)

5-4-2-1. Outline of the statement in Exhibit A2

Exhibit A2 is a publication distributed before the date of the Priority Claim of the Patent and states the following matters.

(2a) (Exhibit A2, page 1678, upper paragraph, left column, lines 7 to 10)

"Method: A double-blind randomized study was conducted in which placebo or carvedilol was administered to 40 patients with idiopathic dilated cardiomyopathy undergoing treatment with digoxin, furosemide, and angiotensin converting enzyme (ACE) inhibitor."

(2b) (Exhibit A2, page 1678, upper paragraph, right column, lines 3 to 11)

"Results: Compared to placebo, carvedilol caused decreases in heart rate, pulmonary artery pressure, and pulmonary artery wedge pressure in a short time. After long-term administration, carvedilol caused increases in cardiac output index and stroke

exercise index at rest and at peak exercise after long-term administration, while causing further decreases in right atrium, pulmonary artery pressure, and pulmonary artery wedge pressure. In addition, long-term carvedilol administration improved the left ventricular ejection fraction at rest (20 ± 7 to 30 ± 12%, p <0.0001), submaximal athletic performance, quality of life, and NYHA functional classification class."

(2c) (Exhibit A2, page 1678, upper paragraph, right column, lines 13 to 18)

"Results: In patients with idiopathic dilated cardiomyopathy, carvedilol decreased heart rate, pulmonary artery pressure, and pulmonary artery wedge pressure by short-term administration, while improving left ventricular contraction function at rest and maximal exercise even for long-term administration, resulting in a decrease in cardiac failure symptoms and an improvement in submaximal athletic performance."

(2d) (Exhibit A2 page 1678, lower paragraph, right column, lines 15 to 17)

"Carvedilol is a novel β-blocker with vasodilating action by α1-receptor antagonism without endogenous sympathomimetic action."

(2e) (Exhibit A2, page 1679, left column, lines 18 to 22)

"Patients: The group under study includes 40 patients (...). These patients continue to suffer from congestive heart failure caused by idiopathic dilated cardiomyopathy for more than 1 year. However, the patients are in a clinically stable state. Thus, the dosing schedule has not changed since one month before the start of the study."

(2f) (Exhibit A2, page 1678, right column, line 22 from the bottom to the next page, left column, line 5)

"In the first phase of the study, short-term hemodynamic effects by placebo or carvedilol (12.5 mg, po.) were evaluated on two consecutive days. ...

In the first phase of the study, short-term hemodynamic effects by placebo or carvedilol (12.5 mg, po.) were evaluated on two consecutive days. ... Following completion of the short-term phase of the study, we resumed the administration of regular doses of digitalis, diuretics, angiotensin converting enzyme inhibitors, and nitrate esters together with placebo or carvedilol to the patients. Carvedilol started from 6.25 mg twice a day, and dosage was increased every week as follows: 6.25 mg three times a day, 12.5 mg twice a day, 12.5 mg three times a day, and finally 25 mg twice a day. ... After the end of the dose escalation phase, patients received the highest dose for at least 3 months.

(2g) (Exhibit A2, page 1680, right column, lines 6 to 8)

"Both the stroke volume and the stroke volume work index increased significantly after long-term therapy, but not by short-term drug administration."

5-4-2-2. Comparison/judgment

In addition to the above statement in (2c), in consideration of the statements of (2a) and (2e), Exhibit A2 may state that "long-term administration of carvedilol to patients with congestive heart failure due to idiopathic dilated cardiomyopathy, on medication with digoxin, furosemide, angiotensin converting enzyme (ACE), caused improvements in left ventricular systolic function at rest and maximal exercise, a decrease in cardiac failure symptoms and an improvement in submaximal athletic performance."

Here, "caused improvements in left ventricular systolic function at rest and

maximal exercise a decrease in cardiac failure symptoms and an improvement in submaximal athletic performance" means that it was effective in treating congestive heart failure and is understood to indicate the use of carvedilol for treatment of congestive heart failure. Furthermore, Exhibit A2 (2d) also states that furosemide is one of diuretics as described in the Patent Specification and carvedilol functions as both β-adrenergic receptor antagonist and α-1 adrenergic receptor antagonist (2d).

From the comparison between Invention 1 and the invention stated in Exhibit A2, they are common in the point of "Use of carvedilol in manufacture of a pharmaceutical agent for congestive heart failure in patients undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin, alone or in conjunction with one or more of other pharmaceutical agents" but differ from each other due to the following different feature.

[The different feature] The different feature is that the Invention is "a pharmaceutical agent for decreasing mortality resulting from congestive heart failure," whereas the cited invention is "a pharmaceutical agent for treating congestive heart failure."

Hereinafter, the different feature will be examined.

The specific limitation requirement corresponding to matters specifying the invention "for decreasing mortality derived from congestive heart failure" in the present invention is not clear from the statement of the scope of claims. Thus, we will consider the detailed description of the Invention. (For example, regarding the "substance" as a pharmaceutical agent, the type of excipient, dosage form, and the like are limited to their respective specific ones. Regarding the "mode of application" of the pharmaceutical agent according to invention 1 to a patient, the treatment modes, such as target patient group, administration interval, and dosage, as well as the application range of adaptive symptoms, application site, and the like are examined.)

The Patent specification states as follows:

"Recently, it has been discovered in clinical studies that pharmaceutical compounds which are dual non-selective β-adrenoceptor and α1-adrenoceptor antagonists, ... , preferably carvedilol, alone or in conjunction with conventional agents, said agents being ACE inhibitors, diuretics, and cardiac glycosides, are effective therapeutic agents for treating CHF. The use of agents such as carvedilol in treating CHF is surprising, since, in general, β-blockers are contraindicated in patients suffering from heart failure, because β-blockers are known to have undesirable cardiodepressive effects. The most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent."

This statement allows the Invention to be recognized as being made based on experimental study performed on carvedilol, one of the beta-blockers conventionally contraindicated in the treatment of congestive heart failure (CHF), to ascertain whether carvedilol is a drug effective for treating CHF; the resulting data of the study were analyzed; and, along with the effectiveness of the treatment of congestive heart failure, results that were not originally assumed; namely, the reduction of mortality rate, were

obtained at the same time.

In consideration of the above statement, the Invention is "a pharmaceutical agent for decreasing mortality resulting from congestive heart failure." However, the Invention cannot be considered as one in which any improvement or ingenious attempt had been carried out in a manner different from just a "treatment of congestive heart failure" in the aspects of therapeutic agent and treatment "for decreasing mortality resulting from congestive heart failure." In other words, the Invention merely uses similar pharmaceutical agents to be used in the "treatment of congestive heart failure" and experimental study is conducted just by administration to patients in accordance with protocols similar to those in the "treatment of congestive heart failure," followed by analyzing the data obtained by the study, and by confirming the effects of causing a decrease in mortality due to congestive heart failure.

Such an understanding can be acknowledged because the administration protocols in "EXPERIMENTAL" in the present specification are basically the same as the administration protocols for "treatment of congestive heart failure" specifically stated in Exhibit A2 and are also basically not different from the administration protocols ((7a), (8c) and (10c) to (10d)) for β-blockers stated in Exhibits A7, A8, and A10, cited in "5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent."

The identification of "a pharmaceutical agent for decreasing mortality derived from congestive heart failure" in the present invention is nothing different from "a pharmaceutical agent for treatment of congestive heart failure" with respect to pharmaceutical agents and basic administration protocols. However, the administration periods are different. In the experiments stated in the present specification, the administration period is 6 to 12 months, whereas experiments in Exhibit A2 state that "after the end of the dose escalation phase, ... at least 3 months" (about 4 months in total, see (2f)). Thus, the following points will be now considered.

From the above statement of Claim 1 after correction, it is obvious that the administration period is not clearly specified in Invention 1. In addition, the following matters are not stated throughout the present specification: the administration period should 6 months or more; "for decreasing mortality derived from congestive heart failure" it must be a dosing period of more than 6 months; and less than 6 months of the administration period exerts no effect "for decreasing mortality derived from congestive heart failure." Further, it is assumed that there is a common general technical knowledge in which the administration period should be "6 to 12 months" for exerting an effect of "reducing the mortality rate" in accordance with the statement of the present specification.

For the administration period, therefore, there is no difference between Invention 1 and the cited invention even though the administration periods are about 4 months in Exhibit A2 and 6 to 12 months in the experiments of the present specification.

Additionally, even if it can be interpreted that the administration period of the pharmaceutical agent of Invention 1 is specified as "6 to 12 months," a person skilled in the art could easily achieve Invention 1 from the content of Exhibit A2.

As recognized in "(C) Use of β-blockers in the treatment of congestive heart failure and the administration period" in "5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent," as a matter of common technical knowledge at the priority date for the Invention, long-term administration is necessary for the effect of β-blocker on congestive heart failure; i.e., improvements in cardiac function and athletic performance. In addition, multiple cases of administration over a period of more than one year have been reported (10c). Based on this fact, in consideration of "the test results for 'long-term administration'" in Exhibit A2 with respect to carvedilol grouped in β-blockers, a person skilled in the art having such common general technical knowledge could naturally understand that the symptom improvement effect by β-blockers would naturally appear even in the administration period of about 4 months as stated in Exhibit A2 or the administration period of about 6 to 12 months.

Thus, it can be said that the statement of Exhibit A 2 would allow a person skilled in the art to understand that any improvement effect on congestive heart failure stated therein could appear even in the administration period of about 6 to 12 months. Even if it can be interpreted that Invention 1 is specified as "6 to 12 months" with respect to the administration period of the pharmaceutical agent, a person skilled in the art could easily achieve Invention 1 from the content of Exhibit A2.

In summary, no substantial difference between Invention 1 and the cited invention can be found in the aspects of therapeutic agent and treatment even in consideration of the aforementioned different point of whether it is "a pharmaceutical agent for decreasing mortality resulting from congestive heart failure" or "a pharmaceutical agent for treating congestive heart failure."

5-4-2-3. Summary

Since Invention 1 is the invention stated in Exhibit A2, Invention 1 falls under Article 29(1)(iii) of the Patent Act and thus cannot obtain a patent. Invention 1 has been patented in breach of the provisions of Article 29(1) of the Patent Act.

5-4-2-4. Inventive step

As stated above, Invention 1 lacks novelty. Here, the inventive step will also be considered.

As stated in the aforementioned "5-4-2-2. Comparison / judgment," the different feature between the cited invention and Invention 1 is whether it is specified as "a pharmaceutical agent for decreasing mortality resulting from congestive heart failure."

In other words, determining whether or not Invention 1 has an inventive step is to determine whether "long-term administration ... caused improvements in left ventricular systolic function at rest and maximal exercise, a decrease in cardiac failure symptoms and an improvement in submaximal athletic performance" in Exhibit A2, or whether a person skilled in the art could have easily achieved the use of carvedilol as a pharmaceutical agent "for decreasing mortality resulting from congestive heart failure," which is stated as being "effective to treat congestive heart failure." We will therefore discuss below based on this point of view.

Based on the common general technical knowledge that a person skilled in the art had as of the priority date for the Invention approved in "5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent." the statement of Exhibit A2 will be examined.

For the indicators recognized by a person skilled in the art as those affecting the survival rate at the priority date for the Invention; i.e., the ventricular contraction function and the left ventricular ejection fraction as stated above, Exhibit A2 states as follows:

"long-term carvedilol administration improved the left ventricular ejection fraction at rest (20 ± 7 to 30 ± 12%, p <0.0001)" (2b)

"Both the stroke volume and the stroke volume work index increased significantly after long-term therapy, but not by short-term drug administration." (2g)

Specifically, the statement of improvement was made about the ventricular contraction function and the left ventricular ejection fraction, which had been recognized by a person skilled in the art as indicators that affected the survival rate of patients with congestive heart failure.

Furthermore, in consideration of the presence of a reported instance of which β-blockers improved the life prognosis (Exhibit A10) even though the situation still made it difficult for a person skilled in the art to recognize any conclusive evidence, a person skilled in the art could have easily conceived of the administration of carvedilol to patients with congestive heart failure, the administration of carvedilol being started at a very small dose as stated in Exhibit A2 and continued over a long period of time on the premise of careful observation, while expecting an improvement in quality of life based on an improvement in cardiac function, which is the purpose of treating congestive heart failure, as well as an improvement in mortality rate.

Furthermore, considering that influences of both the ventricular contraction function and the left ventricular ejection fraction on the survival rate had been common general technical knowledge, the effect of improving mortality by Invention 1 could be within the scope where a person skilled in the art could have inevitably predicted from the common general technical knowledge and the statement in Exhibit A2.

Invention 1 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act. Invention 1 has therefore been patented in breach of the provisions of Article 29(2) of the Patent Act.

Furthermore, even in the presence of a fact of

(a) β-blockers have been contraindicated against congestive heart failure; or

(b) data were not always consistent for the improving effect of β-blockers on the mortality rate of patients, evaluations for β-blockers recognized in "5-4-1 (C) Use of β-blockers in the treatment of congestive heart failure and the administration period" to allow the use of beta-blockers against patients with congestive heart failure are interpreted as evaluations on the results of considering various articles, etc., already known as of the priority date for the Invention based on the above (a) and (b) Here, the evaluations include:

(i) "β-blocker therapy has therefore been regarded as one of the leading treatments for chronic cardiac failure including dilated cardiomyopathy." (10a); and

(ii) "In order to reduce the risk of circulation failure at the time of introduction, it is important to start from a smaller dose and gradually increase the dose. Increasing the dose should be carefully performed in severe cases in which sympathetic nervous activity is accelerated remarkably." (10d).

Based on (a) and (b) above, therefore, it is impossible to recognize that a person skilled in the art "did not try to use the β-blocker as a pharmaceutical agent for congestive heart failure" or "did not try to use it for improving the mortality rate of patients with congestive heart failure."

In addition, the demandee insists that the inventive step of the present invention should be affirmed as follows by citing the statements of Exhibits A9 to A11.

(c) Exhibits A9 and A10 state that β-blocking therapy capable of causing up-regulation of β receptors is attracting attention. Considering this, a person skilled in the art could consider that carvedilol, which had been known not to cause up-regulation, would be not useful for treatment of congestive heart failure.

(d) From the statement of Exhibit A10, it cannot be said that β-blockers are shown to be effective in reducing mortality due to congestive heart failure. In particular, there is no disclosure of "carvedilol" as a β-blocker.

(e) Exhibit A11 states that the cardiac function and the survival rate of patients with cardiac failure are correlated with each other. However, the data represented in Exhibit A11 merely state that patients with lower ejection fraction have a significantly higher mortality rate than patients with higher ejection fraction. Exhibit A11 does not state that an improvement in athletic performance as well as an improvement in left ventricular ejection fraction or the like can enhance the life prognosis of patients with congestive heart failure.

However, as stated below, none of the items can be a basis for affirming the inventive step as stated below.

Regarding (c), even though carvedilol is different from other β blockers, in that carvedilol is not a drug that causes up-regulation of β-receptor, the mechanism of action of β-blockers against patients with congestive heart failure was not always technically clarified. It is considered that it cannot be the reason for avoiding the administration of carvedilol in the first place because "it is not a drug that causes up-regulation of β-receptor." Furthermore, Exhibit A2 states that improvement in the symptoms of congestive heart failure has been shown. This is the same result as other β-blockers stated in Exhibit A10. From this, it can be understood that a person skilled in the art could consider that carvedilol would be useful for treatment of congestive heart failure as well as other β blockers.

Regarding (d), Exhibit A10 states that "An improvement in prognosis of life is also allowed in a report of administration on a yearly basis. However, this report is a study with a few cases. Thus, there is still room for discussion about an improvement in prognosis of life." From this statement, it is clear that it was not recognized that β-blockers were effective in improving mortality. As described in "(C) Use of β-blockers in the treatment of congestive heart failure and the administration period" in

"5-4-1," it can be recognized that, as a common general technical knowledge as of the time of filing this application, for β-blockers, it is recognized that "on the premise that care should start with a small dose at the start of administration, β-blockers were recognized as one of the leading pharmaceutical agents of congestive heart failure." Furthermore, as stated in "5-4-1. (B) Indicators that affect the mortality rate of patients with congestive heart failure," it is recognized that "with regard to patients with congestive heart failure, a person skilled in the art could have recognized that the indicators, such as the contractility of the myocardium, and the left ventricular ejection fraction, influence the survival rate of the patients." In addition to these matters, there is also considered the symptom-improving results of carvedilol administration to patients with convulsive heart failure in Exhibit A2. As stated above, therefore, it can be said that a person skilled in the art could have conceived of administrating carvedilol to patients with congestive heart failure with an expectation of causing a decrease in mortality rate of the patients.

Regarding (e), Exhibit A11 relates to a drug having a mechanism of action different from that of β-blockers. Exhibit A11 states that "it has been widely recognized that ACE inhibitors ameliorate the hemodynamics and symptoms of cardiac failure patients in the short and long terms, extending the survival rate of the patients." (Exhibit A11, page 54, middle column, from the bottom, lines 7 to 4). Exhibit A11 further states that improvements in heart function and symptoms of patients with congestive heart failure correlate with an improvement in prognosis of life. Furthermore, as stated in the above "5-4-1. (B)," Exhibit A9 as well as Exhibit 11 state that an improvement in cardiac function is involved in improving prognosis. The argument of the demandee concerning (e) cannot be accepted.

Furthermore, Invention 1 has no difference from the cited invention as the invention matters specifying the Invention. It is also considered a person skilled in the art could have easily invented Invention 1. Invention 1 is in the range that a person skilled in the art could easily predict. Thus, there is no room for interpretation as a selection invention as the demandee claims.

5-4-3. Regarding Inventions 2 to 4 (the inventions of claims 2 to 4)

5-4-3-1. The contents of the Invention

Invention 2 specifies the administration protocol of carvedilol while referring to the statement of claim 1. Invention 2 is as follows:

[Claim 2] The use of carvedilol as described in claim 1, wherein the use comprises administering a pharmaceutical formulation as first dosages once or twice daily, for a period of from 7 to 28 days, said first dosages each comprising carvedilol in an amount of 3.125 mg or 6.25 mg in a single unit.
[Claim 3] The use of carvedilol as described in claim 1, wherein the use comprises administering a pharmaceutical formulation as once or twice daily, for a period of from 7 to 28 days, said pharmaceutical formulation comprising carvedilol in an amount of 12.5 mg in a single unit.
[Claim 4] The use of carvedilol as described in claim 1, wherein the use comprises administering a pharmaceutical formulation as maintenance dosages once or twice daily,

said maintenance dosages each comprising carvedilol in an amount of 25.0 mg or 50.0 mg in a single unit.

5-4-3-2. Comparison/judgment

On the other hand, the administration protocol stated in Exhibit A2 is as follows:

"Following completion of the short-term phase of the study, ... Carvedilol started from 6.25 mg twice a day, and was increased every week as follows: 6.25 mg three times a day, 12.5 mg twice a day, 12.5 mg three times a day, and finally 25 mg twice a day. ... After the end of the dose escalation phase, patients received the highest dose for at least 3 months." (2f). Thus, the protocol can be organized as follows:

[The administration protocol stated in Exhibit A2]

Week 1	6.25 mg	twice a day
Week 2	6.25 mg	three times a day
Week 3	12.5 mg	twice a day
Week 4	12.5 mg	three times a day
Week 5	25 mg	twice a day

(same dose for the following 3 months)

(1) Regarding Invention 2

Firstly, when comparing the administration protocol stated in Exhibit A2 and the administration protocol stated in Invention 2, they are duplicated in that they include administration of 6.25 mg twice a day from day 1 to day 7.

Thus, the administration protocol stated in Invention 2, "administering a pharmaceutical formulation once or twice daily, for a period of from 7 to 28 days, said pharmaceutical formulation comprising carvedilol in an amount of 12.5 mg in a single unit," is a matter stated in Exhibit A2 and is not different from the protocol stated in Exhibit A2.

(2) Regarding Invention 3

Next, the administration protocol stated in Invention 3 will be examined. In Invention 3, since the timing of performing the protocol during the administration period is not specifically specified, if it is administered at any time during the administration period according to the protocol stated in claim 3, it is interpreted as being included in the scope of Invention 3.

On the basis of such an interpretation, therefore, the administration protocol stated in Exhibit A2 is compared with that stated in Invention 3. Specifically, they may be compared with each other at any time of the administration period. Thus, when comparing Week 3 of Exhibit A2 with Invention 3, both of them overlap in terms of "administering a pharmaceutical formulation containing 12.5 mg of carvedilol in a single unit twice a day for a period of 7 days."

The protocol of "administering a pharmaceutical formulation once or twice daily, for a period of from 7 to 28 days, said pharmaceutical formulation comprising carvedilol in an amount of 12.5 mg in a single unit" stated in Invention 3 is a matter stated in Exhibit A2 and is not different from the protocol stated in Exhibit A2.

(3) Regarding Invention 4

The term "maintenance dosage" stated in Invention 4 can be recognized as a term that means "the final dosage amount" from the statements in this specification of "finally administrating 25.0-mg or 50.0-mg carvedilol per single unit ... as a maintenance dosage" (claim 8), "defining this maintenance dosage as a setting value of 100%, ...," "full daily set doses (maintenance dosage) are administered daily," and so on.

Thus, comparing the administration protocol stated in Exhibit A2 and the administration protocol stated in Invention 2, the final dose of the former is 25 mg and thus the two are overlapped in terms of "administrating a pharmaceutical formulation that contains 25.0-mg carvedilol in a single unit as a maintenance dosage."

Thus, the protocol of "administering a pharmaceutical formulation once or twice daily, for a period of from 7 to 28 days, said pharmaceutical formulation comprising carvedilol in an amount of 12.5 mg in a single unit" stated in Invention 4 is a matter stated in Exhibit A2 and is not different from the protocol stated in Exhibit A2.

5-4-3-3. Summary

As described above, regarding Inventions 2 to 4, matters further added to Invention 1 in those inventions are not different from those described in Exhibit A2. Similar to Invention 1, any of these inventions falls under Article 29(1)(iii) of the Patent Act, and cannot obtain a patent under the provisions of Article 29(2) of the Patent Act.

Thus, Inventions 2 to 4 violate Article 29 of the Patent Law.

5-4-4. Regarding Inventions 5 to 7 (Inventions of claims 5 to 7)

5-4-4-1. Contents of the Invention

Inventions 5 to 7 specify other pharmaceutical agents to be used in combination with carvedilol, referring to the statement of claim 1. These inventions are as follows:

[Claim 5] The use of carvedilol as described in claim 1, wherein the angiotensin converting enzyme is selected from the group consisting of captopril, lisinopril, fosinopril, and enalapril, and any pharmaceutically acceptable salts thereof.
[Claim 6] The use of carvedilol as described in claim 1, wherein the diuretic is selected from the group consisting of hydrochlorothiazide, torasemide, furosemide, and any pharmaceutically acceptable salts thereof.
[Claim 7] The use of carvedilol as described in claim 1, wherein the cardiac glycoside is selected from the group consisting of digoxin, β-methyl-digoxin, and digitoxin.

Here, claim 5 states "the angiotensin converting enzyme (the word "inhibitor" is missing) is ....." In addition, claim 6 states "the diuretic is ...." In the statement of claim 1 after correction, two "angiotensin converting enzyme inhibitors" and two "diuretics" are described, respectively. From such a statement alone, it is not clear which the above wording of each claim is pointing to. Considering the circumstances of the request for correction and the like, it is interpreted that the phrase "the pharmaceutical agent is .... angiotensin converting enzyme inhibitors, diuretics, and ..." is stated in the latter part of claim 1. It is therefore interpreted as stated below.

5-4-4-2. Examination

In ordinary treatment, it is properly adopted to use a plurality of pharmaceutical agents effective for the same disease or symptom unless special circumstances exist. For example, Exhibit A7 states that "Vasodilator: (a) ACE inhibitor ... examples of NYHA classes II to IV are used in combination with conventional pharmaceutical agents to improve prognosis." (Exhibit A7, page 316, right column, lines 17 to 21). Treatment of congestive heart failure is also adequately adopted in combination with multiple drugs as appropriate.

Furthermore, the present specification includes no statement for clarifying what kind of effect is exerted concretely by being used in combination.

Thus, in addition to the matters specifying Invention 1, additional matters newly specified in Inventions 5 to 7 could be easily made by a person skilled in the art.

5-4-4-3. Summary

As stated above, in Inventions 5 to 7, additional matters further added to Invention 1 could be easily made by a person skilled in the art. Further, as stated above, Invention 1 is an invention stated in Exhibit A2 and could be easily invented by a person skilled in the art from the statement of Exhibit A2. Invention 2 has therefore been patented in breach of the provisions of Article 29(2) of the Patent Act.

All of the Inventions 5 to 7 were therefore made in violation of Article 29(2) of the Patent Law.

5-4-5. Regarding Invention 8 (Invention of claim 8)

5-4-5-1. Contents of the Invention

Invention 8 is stated in the form of an independent claim and is specified by the following matters:

"[Claim 8] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin according to the regimen of:

(a) administrating a pharmaceutical formulation that contains 3.125-mg or 6.25-mg carvedilol per single unit for a period of 7 to 28 days, once or twice daily;

(b) subsequently administrating a pharmaceutical formulation that contains 12.5-mg carvedilol per single unit for an additional period of 7 to 28 days, once or twice daily; and

(c) finally administrating a pharmaceutical formulation that contains 25.0-mg or 50.0-mg carvedilol per single unit, once or twice daily as a maintenance dosage."

5-4-5-2. Comparison/Examination

In the above "5-4-2. Regarding Invention 1," just like comparison with Invention 1, the cited invention (the invention stated in Exhibit A2) is compared with

Invention 8. Here, the cited invention is "long-term administration of carvedilol to patients with congestive heart failure due to idiopathic dilated cardiomyopathy, undergoing treatment with digoxin, furosemide, angiotensin converting enzyme ACE) inhibitor, caused improvements in left ventricular systolic function at rest and maximal exercise, a decrease in cardiac failure symptoms and an improvement in submaximal athletic performance." The cited invention and Invention 1 are identical in that they state
"use of carvedilol in manufacture of a pharmaceutical agent for congestive heart failure in patients undergoing background therapy with diuretic, angiotensin converting enzyme inhibitor, and/or digoxin,"
but they are different from each other in the following points:
[Different feature 1] Invention 8 states "a pharmaceutical agent for decreasing mortality resulting from congestive heart failure," whereas the cited invention states "a pharmaceutical agent for treating congestive heart failure."
[Different feature 2] In Invention 8, the administration protocol is specified as follows, whereas such a specified feature is not made in the cited invention:
(a) administrating a pharmaceutical formulation that contains 3.125-mg or 6.25-mg carvedilol per single unit for a period of 7 to 28 days, once or twice daily;,
(b) subsequently administrating a pharmaceutical formulation that contains 12.5-mg carvedilol per single unit for an additional period of 7 to 28 days, once or twice daily; and
(c) finally administrating a pharmaceutical formulation that contains 25.0-mg or 50.0-mg carvedilol per single unit, once or twice daily as a maintenance dosage.

The above different features will be examined.

Regarding Different feature 1, as stated in "5-4-2. Regarding Invention 1," there is no substantial difference between Invention 8 and the cited invention. Thus, Invention 8 could be easily made by a person skilled in the art.

Then, different feature 2 will be examined.

As stated in "5-4-3. Regarding the Inventions 2 to 4," Exhibit A2 (2f) states the following protocol:

[The administration protocol stated in Exhibit A2]

Week 1	6.25 mg	twice a day
Week 2	6.25 mg	three times a day
Week 3	12.5 mg	twice a day
Week 4	12.5 mg	three times a day
Week 5	25 mg	twice a day

(same dose for the following 3 months)

Comparing this protocol with the protocol of Invention 8, both of them include that the first day dosage is 6.25 mg twice a day. They also include a final maintenance dosage of 50 mg/day. Furthermore, there is no difference in dose escalation of the drug during that time. However, the specific dose escalation schemes are different from each other.

However, at the beginning of dosing as stated above, the method of gradually increasing from a small dose is a procedure of common general technical knowledge for

β-blockers as recognized in the above "5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent."
(Exhibits A7, 8, and 10 (see (7a), (8c), and (10c) to (10d)))

The dose escalation scheme of Invention 8 is based on the common general technical knowledge concerning the method of administering β-blockers. Moreover, there is no difference in the first day dosage and the final maintenance dosage stated in Exhibit A2. Thus, a person skilled in the art could appropriately create the dose escalation scheme of Invention 8 based on the statement of Exhibit A2 with no particular inventiveness.

5-4-5-3. Summary

Invention 8 could have been easily invented by a person skilled in the art based on the statement of Exhibit A2 and the common general technical knowledge. Thus, Invention 8 falls under the provisions of Article 29(2) and violates the provisions of Article 29 of the Patent Act.

5-4-6. Regarding Invention 9 (Invention of claim 9)

5-4-6-1. Contents of the Invention

Invention 9 cites claim 8 and specifies the administration of carvedilol in combination with any of other pharmaceutical agents, the contents of which are as follows:

[Claim 9] The use of carvedilol according to claim 8, wherein the use comprises administration of carvedilol alone or in combination with one or more of other pharmaceutical agents, and the pharmaceutical agent is selected from angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides.

5-4-6-2. Comparison/judgment

It is already stated in "5-4-4. Regarding Inventions 5 to 7" that administering carvedilol in combination with another pharmaceutical agent, such as angiotensin converting enzyme inhibitor, cannot be an invention having inventive step.

Thus, Invention 9 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act.

5-4-7. Regarding Invention 10 (Invention of claim 10)

5-4-7-1. Contents of the Invention

Invention 10 cites claim 1 and further identifies the administration protocol, the contents of which are as follows:

[Claim 10] The use of carvedilol according to claim 1, wherein carvedilol is used for the preparation of a medicament for treating congestive heart failure and the medicament can be administered at a daily maintenance dosage of 10 to 100-mg carvedilol, and the medicament is administered following an incremental dosing scheme including a

three-stage administration regimen, the scheme comprising:

a first regimen in which 10 to 30% of the daily maintenance dosage of carvedilol is administered for a period of 7 to 28 days;

a second regimen in which 20 to 70% of the daily maintenance dosage of carvedilol is administered for a period of 7 to 28 days; and

a third regimen in which 100% of the daily maintenance dosage of carvedilol is administered, the third regime being initiated after the end of the second regimen.

5-4-7-2. Comparison/judgment

The administration protocol stated in Invention 10 is as follows:

a daily maintenance dosage is 10 to 100-mg carvedilol;

a first regimen is the administration of 10 to 30% of the daily maintenance dosage for a period of 7 to 28 days;

a second regimen is the administration of 20 to 70% of the daily maintenance dosage for a period of 7 to 28 days; and

a third regimen is the administration of 100% of the daily maintenance dosage.

In contrast, the administration protocol stated in Exhibit A2 (2f) is as follows:

Week 1	6.25 mg	twice a day
Week 2	6.25 mg	three times a day
Week 3	12.5 mg	twice a day
Week 4	12.5 mg	three times a day
Week 5	25 mg	twice a day

(same dose for the following 3 months)

Comparing the protocols, both include a daily dosage of 12.5 mg on the first day (corresponding to 25% of a maintenance dosage of 50 mg/day) and also include a final maintenance dosage of 50 mg/day. Furthermore, there is no difference in dose escalation of the drug in the course of the administration period, but the specific dose escalation schemes are different.

However, at the beginning of dosing as stated above, the method of gradually increasing from a small dose is a procedure of common general technical knowledge for β-blockers as recognized in the above "5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent."
(Exhibits A7, 8, and 10 (see (7a), (8c), and (10c) to (10d))

The dose escalation scheme of Invention 10 is based on the common general technical knowledge concerning the method of administering β-blockers. Moreover, there is no difference in the first day dosage and the final maintenance dosage stated in Exhibit A2. Thus, a person skilled in the art could appropriately create the dose escalation scheme of Invention 10 based on the statement of Exhibit A2 with no particular inventiveness.

5-4-7-3. Summary

Invention 10 could have been easily invented by a person skilled in the art based on the statement of Exhibit A2 and the common general technical knowledge.

Thus, Invention 10 falls under the provisions of Article 29(2) and violates the provisions of Article 29 of the Patent Act.

6. Closing

As stated above, therefore, Inventions 1 to 4 are inventions stated in Exhibit A2. In addition, Inventions 1 to 10 are inventions that could be easily invented by a person skilled in the art based on the invention stated in Exhibit A2 and the common general technical knowledge as of the priority date for the Invention. Each of Inventions 1 to 10 has therefore been patented in breach of the provisions of Article 29 of the Patent Act. The Patent falls under Article 123(1)(ii) of the Patent Act and should therefore be invalidated.

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

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

March 4, 2009

Chief administrative judge:	HOSHINO, Shoei
Administrative judge:	TANIGUCHI, Hiroshi
Administrative judge:	TSUKANAKA, Tetsuo