Trial decision

Invalidation No. 2007-800192

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The decision on the case of the patent invalidation trial between the above parties on Japanese Patent No. 3546058, entitled "Use of carbazole compounds for the treatment of congestive heart failure," dated March 4, 2009 came with a court decision of revocation of the trial decision (2009 (Gyo-Ke) 10101, and rendition of decision on June 8, 2009) at the Intellectual Property High Court, the case was proceeded further, and another trial decision was handed down 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

(1) 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.

(2) 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 registered holder was transferred to Roche Therapeutics Incorporated F. Hoffmann-La Roche Aktiengesellschaft

and further, on the same date, the registered holder was transferred to Daichi Sankyo Co., Ltd. Thus, Daichi Sankyo Co., Ltd. takes over the proceedings of this case.

(3) 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.

(4) The first oral proceeding was conducted on August 27, 2009. 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 October 27, 2008. Subsequently, the demandant filed a written statement on September 22, 2008, while the demandee field written statements on September 19 and October 27, 2008, respectively.

(5) The trial decision was made on March 4, 2009: "The correction shall be approved. The patent regarding the inventions according to Claims 1 to 10 of Japanese Patent No. 3546058 is invalidated."

(6) Against this, the demandee filed a suit for revocation of the trial decision to the Intellectual Property High Court on April 13, 2009 (2009 (Gyo-Ke) 10101) and then requested the trial for correction on May 12, 2008 (Correction 2009-390065). Then, on June 8, 2009 the Intellectual Property High Court made the decision of revocation of

the trial decision, based on the provisions of Article 181(2) of the Patent Act, and returned the case to the Japan Patent Office.

(7) After the case was returned, the period for requesting correction was specified based on the provisions of Article 134(2) of the Patent Act. On June 23, 2009. Within the period, the demandee filed a written correction request referring to the corrected specification attached to the written demand of the above trial for correction. Against this, the demandant for the trial for invalidation filed a written refutation on August 4, 2009. After that, the demandee filed a written reply on February 26, 2010.

2. Request for correction

(1) Contents of correction

(Correction a)

In claim 1 of the scope of the invention, "mammals" is corrected to read as follows: "mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin."

(Correction b)

In claim 1 of the scope of the invention, "congestive heart failure" is corrected to read as follows: "ischemic and non-ischemic congestive heart failure."

(Correction c)

c. In claim 1 of the scope of the invention, "decreasing mortality" is corrected to read as follows: "decreasing mortality ... substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms."

(Correction d)

d. In claim 1 of the scope of the invention, "a pharmaceutical agent" is corrected to read as follows: "the pharmaceutical agent being administered for six months or more after a low-dose challenge period."

(Correction e)

e. In claim 8 of the scope of the invention, "mammals" is corrected to read as follows: "mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin."

(Correction f)

f. In claim 8 of the scope of the invention, "congestive heart failure" is corrected to read as follows: "ischemic and non-ischemic congestive heart failure."

(Correction g)

g. In claim 8 of the scope of the invention, "decreasing mortality" is corrected to read as follows: "decreasing mortality ... substantially equally in ischemic and non-ischemic heart failure, and decreasing mortality similarly substantially in class III-IV symptoms."

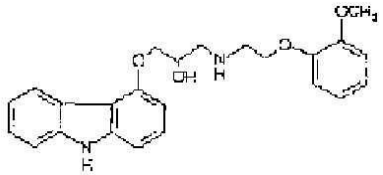
(Correction h)

h. In claim 8 of the scope of the invention, "a pharmaceutical agent" is corrected to read as follows: "a pharmaceutical agent to be administered for six months or more after a challenge period of low-dose carvedilol."

In other words, according to Corrections a to d as stated above, claim 1 is corrected to read as below.

<Claim 1 before correction>

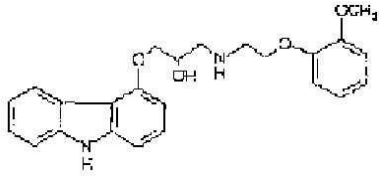
"[Claim 1] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from congestive heart failure in mammals alone or in conjunction with one or more of other pharmaceutical agents, the cardiolol having the following structure of both β-adrenoceptor antagonist and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



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

<Claim 1 after collection>

"[Claim 1] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from ischemic and non-ischemic congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms alone or in conjunction with one or more of other pharmaceutical agents, the pharmaceutical agent being administered for six months or more after a low-dose challenge period, the cardiolol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist:



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

Furthermore, according to Corrections e to h as stated above, claim 8 is corrected to read as below.

<Claim 8 before correction>

"[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 7to 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 for an additional period of 7 to 28 days, once or twice daily as a maintenance dosage."

<Claim 8 after correction>

"[Claim 8] Use of carvedilol in manufacture of a pharmaceutical agent for decreasing mortality resulting from ischemic and non-ischemic congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms, the pharmaceutical agent being administered for six months or more after a low-dose challenge period 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 7to 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 for an additional period of 7 to 28 days, once or twice daily as a maintenance dosage."

Although not stated in Corrections a to h as stated above, claims 2 to 7 and 10 of the scope of claims in the corrected specification cite claim 1. In addition, claim 9 cites claim 8. Thus, correction has been made on these claims in a manner similar to claim 1 or 8.

(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 e 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 e 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 carbazole to patients, states that targets of the administration are 2 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 e 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.

Corrections b and f correct "congestive heart failure" stated in Claims 1 and 8 before correction to "ischemic and non-ischemic congestive heart failure," respectively. However, such corrections do not cause a change in substantial meaning, because congestive heart failure is either of ischemic and non-ischemic. Thus, the

corrections fall under the clarification of an ambiguous description. Corrections b and f are therefore 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.

Furthermore, the demandee insists that Corrections b and f are intended for restriction of the scope of claims for patent. As a result of the body's examination, however, the body determined that Corrections b and f should be interrupted as stated above.

Next, Corrections c and g correct "decreasing mortality" stated in Claims 1 and 8 before correction to "decreasing mortality ... substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms", respectively. The first half of the correction, "decreasing mortality ... substantially equally in ischemic and non-ischemic congestive heart failure," does not cause a change in substantial meaning because congestive heart failure is either of ischemic and non-ischemic, as stated above. In addition, the latter half of the correction, "and decreasing mortality similarly substantially in class III-IV symptoms" corresponds to one that intends to restrict the scope of claims for patent as a whole because the severity of congestive heart failure is classified into four stages of classes I to IV and the correction allows the invention to be limited to three stages of II to IV among them. As a whole, therefore, each of Corrections c and g corresponds to one that restricts the scope of claims for patent. Thus, Corrections c and g do not substantially enlarge or modify the scope of claims of the patent.

In "EXPERIMENTAL" representing specific examples of carvedilol given to patients stated in the detailed description of the invention in the present patent specification, patients with severity levels II to IV are targeted (Gazette containing the Patent, page 7, line 7 and Table 1 on page 8). Thus, Corrections c and g as stated above are within the scope of the matters stated in the specification attached to the application and do not substantially enlarge or modify the scope of claims of the patent.

Corrections d and h correct "a pharmaceutical agent" stated in Claims 1 and 8 before correction to "a pharmaceutical agent to be administered for six months or more after a challenge period of low-dose carvedilol," respectively.

The corrections restrict the statements of the period of administrating a pharmaceutical agent, which is not restricted before correction, to "six months or more after a low-dose challenge period" after correction. Thus, both Corrections d and h intend to restrict the scope of claims for patent.

In "EXPERIMENTAL" representing specific examples of carvedilol given to patients stated in the detailed description of the invention in the present patent specification, it is stated "The maintenance phase of each study ranged from six to 12 months," (Gazette containing the Patent, page 8, line 6) and these corrections do not substantially enlarge or modify the scope of claims of the patent.

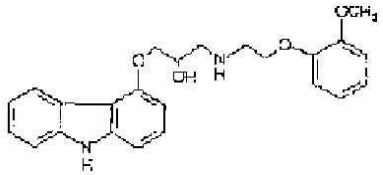
(3) Summary

A described above, each of Corrections a to h as stated above 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 to h shall be 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 ischemic and non-ischemic congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms alone or in conjunction with one or more of other pharmaceutical agents, the pharmaceutical agent being administered for six months or more after a low-dose challenge period, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist:



wherein the pharmaceutical agent is selected from angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides.
[Claim 2] The use of carvedilol as described in claim 1, wherein the use comprising administering to said patient first dosages once or twice daily, for a period of 7 to 28 days, said first dosages each comprising carvedilol in an amount of 3.125 mg or 6.25 mg.
[Claim 3] The use of carvedilol as described in claim 1, wherein the use comprises administering to said patient first dosages once or twice daily, for a period of 7 to 28 days, said first dosages each comprising carvedilol in an amount of 12.5 mg.
[Claim 4] The use of carvedilol as described in claim 1, wherein the use comprises administering to said patient maintenance dosages once or twice daily, said maintenance dosages each comprising carvedilol in an amount of 25.0 mg or 50.0 mg.
[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, or any pharmaceutically acceptable salt 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, or any pharmaceutically acceptable salt 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 ischemic and non-ischemic congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms, the pharmaceutical agent being administered for six months or more after a low-dose challenge period 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 7to 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 for an additional period of 7 to 28 days, 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 is administered following a three-stage incremental application regimen including a three-stage application scheme, 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 correctively referred to as "the Invention."

4. Overview of the parties' allegations

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 be therefore 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)."

Reasons A to D are 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 each of them does not correspond 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

Any 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 have been 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 1993
Exhibit A8: Today's Therapy 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

Exhibit A13: Medical Statistics Q&A, published in October 30, 1987
Exhibit 14: Guidelines on the Statistical Analysis of Clinical Studies, the Japanese Ministry of Health and Welfare, Ministry of Pharmaceutical Affairs, New Medicine Section Manager, March 4, 1992
Exhibit 15: Clinical Trials 2003 YakujiNippo,Ltd.
(Reference materials submitted by Demandant)

1. "Introduction to Statistics in Medical Research", page 106, Table 7
2. "Clinical Trials 20032", page 19
3. 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 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 proven that there is a correlation between the two. Improvement of the mortality rate could not be predicted from the effects of improving carvedilol hemodynamics and exercise capacity.

(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 mortality improvement effect of carvedilol is quite remarkable, far beyond expectation.

(4) The Invention has novelty in "decreasing mortality ... substantially equally in ischemic and non-ischemic congestive heart failure" and "decreasing mortality similarly substantially in class III-IV symptoms."

(5) The Invention is specified by "administered for six months or more after a low-dose challenge period" to make the Invention different from the invention stated in Exhibit A2. This different feature is also a substantial different feature in a practical sense.

(6) The hemodynamic parameters and the like only show improvement tendency. Carvedilol is a β-blocker conventionally contraindicated against heart failure and having utility not established at all in clinical practice. It was completely unknown whether it would exacerbate or improve the mortality rate. From the results of the examination of Exhibit A2, it is not considered to be administered for more than six months after a challenge period of low-dose carvedilol.

(7) The use of carvedilol for "decreasing mortality resulting from ischemic and non-ischemic congestive heart failure ... substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms" in the Patent is clearly different from the use of carvedilol for "improving hemodynamic parameters and the like" stated in Exhibit A2.

(8) Before the priority date of the Patent, it was only to be used with extreme caution, and only a doctor who had experience of using β-blockers for patients with heart failure was permitted to use carvedilol with extreme caution. Thus, it is hardly conceivable to administer β-blocker carvedilol for a period of more than 4 months based on the results of the study stated in Evidence A2 only showing a tendency to improve hemodynamic parameters or the like.

(9) Based on the test results in the present specification, β-blockers to which carvedilol belongs have been positioned as class-II pharmaceutical agents. In other words, the results allowed wide use of β-blockers as pharmaceutical agents for heart failure, indicating that the findings from the study of the present patent specification were beyond the prediction of a person skilled in the art.

(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
Exhibit B16: Today's Therapy 1993 (Volume 35), p. 314-317, February 15, 1994
Exhibit B17: Today's Therapy 1993 (Volume 36), p. 312-313, February 15, 1994
Exhibit B18: Medical Products in the Treatment of Cardiac Failure, p. 263-275, Nov. 1995 (published in June, 1995)
Exhibit B19: Clinical Practice Guideline (Number 11), Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic Dysfunction, "6 Pharmacological Management", p. 49-66, June 1994 (published in June 1994)
Exhibit B20: ACC/AHA Task Force Report, Guidelines for the Evaluation and Management of Heart Fai lure, Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee

on Evaluation and Management of Heart Failure), p. 2764-2782, Nov. 1995 (published in October 1, 1995)

(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 that "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 admitted. With such correction, claims 1 to 8 and 10 includes 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 that "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, an "invention of process." Thus, the category of the invention is clear and thus the statement of claim 1 cannot be said that it violates 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) of the Patent Act.

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

5-4-1. Technical knowledge at 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 is common as general knowledge at 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 the content in accordance with the actual situation, and organize and briefly describe necessary information" (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 a common general technical knowledge of a person killed in the art at the date of the Priority Claim of the Patent.

(A) <u>Purpose of treating congestive heart failure</u>

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 most clinically convenient. ... 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 A8, A9, and A11, 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) <u>Indicators that affect the mortality rate of patients with congestive heart failure</u>

Exhibits A9 and A11 include the 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 step down 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 how significant the morphological findings and left ventricular hemodynamic index are. In patients with ejection fraction of 35.5% or more, the cumulative survival rates 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 were 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 deaths. 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%. As a result, 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 sufficiently gain insight into prognosis for the treatment."

From the description of these Exhibits A9 and A11, it can be understood that, at the priority date for the Invention, "with regard to patients with congestive heart failure, a person skilled in the art had been 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

Exhibit A7, A8, and A10 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. Blocking agents: 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 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. made 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 ofβ-receptor blockers was confirmed by long-term administration of β-blocker by additional test. β-blocker therapy has been therefore 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 that β-blockers were effective. On the other hand, Table 2 summarizes the reports thatβ-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 at the longest. 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 administered 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 be therefore 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 Example 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
ブロッカー中止　Canceled blocker
平均１９ヵ月　19 months in average
数ヵ月　Several months
平均１４ヵ月　14 months in average
３ヵ月　Three months

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
日　　Day
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 it is often able to withstand the usual dose (40 to 80 mg/day in metoprolol)."

From the statements in Exhibits A7, A8, and A10, 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 at 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 quality of life: 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 had been 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-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 $30 \pm 12\%$, $p < 0.0001$), 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 24)
"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." All the patients are with symptomatic failure (New York Heart Association (NYHA) Functional Class II or III), ..."
(2f) (Exhibit A2, page 1678, right column, line 2 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 in 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 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 twice. ... 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

Interpreting Exhibit A2 by supplementing the statements of (2a), (2e) and (2f) in addition to the statement of the above (2c), the cited invention is that "at least three-month administration of carvedilol after a dose escalation phase to patients with congestive heart failure due to idiopathic dilated cardiomyopathy, undergoing treatment with digoxin, furosemide, angiotensin converting enzyme ACE) inhibitor, the patient being in New York Heart Association (NYHA) Functional Class II or III, caused improvements in left ventricular systolic function at rest and maximal exercise, reduction in heart failure symptoms, and improvement in submaximal exercise tolerance."

Here, "caused improvements in left ventricular systolic function at rest and maximal exercise" 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). The patients targeted by Exhibit A2 are patients with congestive heart failure caused by idiopathic dilated cardiomyopathy. Such patients are classified as non-ischemic.

In other words, the statement of Exhibit A2 can be read as follows using the terms of Invention 1:

"A pharmaceutical agent for treating patients with non-ischemic congestive heart failure in class II or III undergoing background therapy with diuretic, angiotensin converting enzyme inhibitor, and/or digoxin, the pharmaceutical agent being carvedilol being administered for at least three-month after a dose escalation phase."

From the comparison between Invention 1 and the invention stated in Exhibit A2, they are common in the point of "Use of carvedilol having the structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist 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" but are different from each other due to the following different feature.

[Different feature] Invention 1 is "a pharmaceutical agent for decreasing mortality resulting from ischemic and non-ischemic congestive heart failure ... substantially equally in ischemic and non-ischemic heart failure, and decreasing mortality similarly substantially in class III-IV symptoms, the pharmaceutical agent being administered for six months or more after a low-dose challenge period," whereas the invention stated in Exhibit A2 is "a pharmaceutical agent for treating a patient with non-ischemic congestive heart failure having a symptom in class II or III, the patient being given at least three-month administration after a dose escalation phase."

Hereinafter, the different feature will be examined.

First, regarding the matters specifying the Invention 1: "decreasing mortality resulting from congestive heart failure" and "decreasing mortality similarly substantially in class III-IV symptoms," these matters are 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, in particular the compounds of Formula I, 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. Furthermore, this result is present across all classifications of CHF and both etiologies (eschemic and non-eschemic)." (Gazette containing the Patent, from page 4, line 41 to page 5, line 4)

In consideration of the above statement, it can be understood that Invention 1 was made based on the following facts: experiments were conducted to ascertain whether carvedilol, one of the β-blockers conventionally contraindicated in the treatment of CHF (congestive heart failure), is an effective pharmaceutical agent for treating CHF; by analyzing the resulting data, initially unexpected results, such as a decrease in mortality rate as well as the effectiveness of treatment of congestive heart failure, could be simultaneously obtained; and the results were similar in all classifications of the severity class and in both ischemic and non-ischemic etiologies.

As stated above, Invention 1 is based on the identification of "decreasing mortality derived from congestive heart failure" and "decreasing mortality similarly in class III-IV symptoms." However, it can be understood that the Invention was made as stated below. It cannot be understood that some improvement or ingenuity in pharmaceutical agents, treatment modes, or the like have been made in a manner different from the case of mere "treatment of congestive heart failure" in order to "decrease mortality due to congestive heart failure" for both etiologic patients or each severity patient. Just the same pharmaceutical agents used for "treatment of congestive heart failure" were used. Experiments were done by administering them to patients according to protocols similar to those for "treatment of congestive heart failure" and the resulting data was analyzed. A decrease in mortality caused by congestive heart failure was confirmed as an effect.

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 for β-blockers stated in Exhibits A7, A8, and A10 ((7a), (8c) and (10c) to (10d)), cited in "5-4-1. Technical knowledge at the date of the Priority Claim of the Patent."

The identification of "decreasing mortality resulting from congestive heart failure" and "decreasing mortality similarly substantially in class III-IV symptoms" in Invention 1 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 states that "after the end of the dose escalation phase, ... at least 3 months."

Then, it can be considered as a specific limitation requirement by being specified as "decreasing mortality resulting from congestive heart failure" and "decreasing mortality similarly substantially in class III-IV symptoms"; in Invention 1 it is only stated that it is "being administered for six months or more after a low-dose challenge period," which is specified separately in Invention 1.

However, such a requirement has no critical significance necessary, because of the following: As stated above, in the statement of the present specification, basically, the administration protocol is basically conventionally used. Then, the administration experiment using such a protocol was set with an administration period of 6 to 12 months. Analysis of the resulting data revealed a significant difference in the reduction of mortality. However, it cannot be said from the statement of the present specification that it was shown that it is impossible to exert the effect of decreasing the mortality unless the administration period is necessarily more than 6 months. In addition, it cannot be said that if the administration period is shorter than that, it can show only therapeutic effect. Thus, the administration period of "six months or more after a low-dose challenge period" in Invention 1 cannot be regarded as a requirement having critical significance necessary for decreasing mortality. This point will be stated further later.

Next, consideration will be given to the substantive meanings of "ischemic and non-ischemic congestive heart failure" and "in class III-IV symptoms" as well as the etiology and severity, which are specified in Invention 1.

Invention 1 states that "decreasing mortality ... substantially equally in ischemic and non-ischemic congestive heart failure." From such wording only, it is possible to understand as follows: For example, Invention 1 includes only pharmaceutical agents that show similar pharmacological effects between when administered to patients with ischemic congestive heart failure and when administered to patients with non-ischemic congestive heart failure. Pharmaceutical agents that show different medicinal effects are not included in Invention 1. It is also possible to say that the requirement "six months or more after a low-dose challenge period" is a necessary requirement for "decreasing similarly substantially."

However, such wording cannot be clearly found in the present specification. As stated above, in the experiment stated in the specification, the requirement "six months or more after a low-dose challenge period" is not stated to have the critical significance necessary for the reduction of mortality. Even more, the mortality is not stated to be a necessary requirement to "decreasing similarly substantially" in ischemic congestive heart failure and non-ischemic congestive heart failure. In consideration of the statement of the present specification, interpretation with the above-mentioned wording cannot be adopted.

Then, the substantive meanings of "decreasing mortality ... substantially equally in ischemic and non-ischemic congestive heart failure" is that the pharmaceutical agent causes a substantial decrease in mortality in both patients with ischemic congestive heart failure and patients with non-ischemic congestive heart failure, similarly. In other words, as an aspect of Invention 1, a case where the pharmaceutical agent is administered to patients with ischemic congestive heart failure and a case where administration is administered to patients with non-ischemic congestive heart failure are both included in one aspect. These cases should be interpreted as those that cause a decrease in mortality.

Furthermore, it is interpreted that "decreasing mortality similarly in class III-IV symptoms" stated in Invention 1 include as the aspect of Invention 1 the administration of the pharmaceutical agent to any one of patients with a severity of class II, patients with a severity of class III, and patients with a severity of class I.

Furthermore, the invention stated in Exhibit A2 covers patients with non-ischemic congestive heart failure, which is congestive heart failure caused by idiopathic dilated cardiomyopathy. However, the administration of pharmaceutical agents to such patients is included in one aspect of Invention 1. In Invention 1, etiology is specified as "ischemic and non-ischemic congestive heart failure." Thus, there is no substantial difference between Invention 1 and the invention stated in Exhibit A2. Regarding the degree of severity, furthermore, the invention stated in Exhibit A2 was also conducted on patients with class II or III. This case can be also included in the aspect of Invention 1. In Invention 1, furthermore, the severity is specified as "in class III-IV symptoms." Thus, Invention 1 and the invention stated in Exhibit A2 cannot be made to be substantially different from each other.

As described, above, Invention 1 is specified by "decreasing mortality resulting from congestive heart failure" and "decreasing mortality similarly substantially in class III-IV symptoms," whereas the invention stated in Exhibit A2 relates to "a pharmaceutical agent for treating a patient with non-ischemic congestive heart failure." A substantial difference between them from the viewpoint of "pharmaceutical agent" and "mode of application" is only one point as follows: "being administered for six months or more after a low-dose challenge period" in Invention 1, whereas "being given at least three-month administration after a dose escalation phase" in the invention stated in Exhibit A2.

Here again, differences between Invention 1 and the invention stated in Exhibit A2 are focused on substantial differences and are stated as follows:

[Substantial difference] Invention 1 is "a pharmaceutical agent for decreasing mortality of congestive heart failure, the pharmaceutical agent being administered for six months or more after a low-dose challenge period," whereas the invention stated in Exhibit A2 is "a pharmaceutical agent for treating congestive heart failure, the pharmaceutical agent being given at least three-month administration after a dose escalation phase."

Thus, Invention 1 and the invention stated in Exhibit A2 are substantially different from each other. The patented invention 1 cannot be said to be the invention stated in Exhibit A2 and cannot fall under Article A29(1)(iii).

Therefore, we will examine the substantial difference for the inventive step.

First, we will examine whether a person skilled in the art could easily conceive the administration of carvedilol, which had been administered for "treatment of congestive heart failure," to cause a decrease in mortality of patients in Exhibit A2.

The statement of Exhibit A2 will be considered based on common general technical knowledge which a person skilled in the art had at the priority date of the patented invention approved in the above "5-4-1. Technical knowledge at the date of the Priority Claim of the Patent."

As stated above, Exhibit A2 states parameters recognized as those that affect the survival rate by a person skilled in the art at the priority date of the patented invention; i.e., the ventricular systolic function and the left ventricular ejection fraction, as follows:

"Long-term carvedilol administration improved the left ventricular ejection fraction at rest (20 ± 7 to $30 \pm 12\%$, $p < 0.0001$)." (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 the 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 caused a person skilled in the art difficulty in recognizing 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, 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." (10b); 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 it for improving the mortality rate of patients with congestive heart failure" and the like. If it is publicly approved as a pharmaceutical agent, it is necessary to establish its usability in order to be distributed and sold. As a preliminary step, it is understood that there is a stage in which various kinds of data are provided, the data serving as sufficient motivation for using a certain pharmaceutical agent in a specific therapeutic application. Even at such a stage, it is understood that it is sufficient for recalling a technical idea that a certain pharmaceutical agent would be useful for a particular therapeutic application. Thus, in order to discuss the easily-conceived property of the invention, there is no necessity that the usefulness is established. Based on (a) and (b) above, therefore, it is impossible to recognize that a person skilled in the art "did not try to use it for improving the mortality rate of patients with congestive heart failure" and the like.

Next, the administration period will be examined.

As recognized in "(C) Use of β-blockers in the treatment of congestive heart failure and the administration period thereof" of "5-4-1. Technical knowledge as of the date of the Priority Claim of the Patent," as a matter of common general technical knowledge before the priority date of the patented invention, the effects of β-blocker on

congestive heart failure; i.e., the effects of improving cardiac function and improving exercise capacity, require long-term administration (8c). Furthermore, long-term administration on a yearly basis had already been carried out (10c). However, a person skilled in the art could not recognize the yearly-based administration as being confirmed. In contrast, there was also a report that life prognosis improved (10b). If a person skilled in the art based on such common general technical knowledge could touch the "test results for "long-term administration"" in Exhibit A2 for carvedilol belonging to a class of β-blockers and, even if the specific administration period described in the results is at least three months after the end of dose escalation phase, could expect more reliable effects and an improvement in life prognosis. Then, a person skilled in the art could start the administration of a pharmaceutical agent with a very small dose at the beginning of dosing and then, on the premise of careful observation, further administer it for a period close to the annual unit, which had already reported dosing for more than three months, for example more than six months, as described in Exhibit A2.

As stated above, furthermore, the statement of the present specification does not indicate the following matters: The effect of decreasing the mortality rate cannot be attained unless the dosing period is more than six months and only the therapeutic effect can be obtained if it is shorter than that. Invention 1 states "being administered for six months or more after a low-dose challenge period." However, such an administration period cannot be regarded as a requirement having critical significance that is indispensable for achieving the effect of decreasing the mortality. Furthermore, therefore, it is obvious that Invention 1 does not find a novel administration mode of "being administered for six months or more after a low-dose challenge period" for "decreasing mortality." Thus, there is no need of considering whether a person killed in the art could have easily conceived of "for decreasing mortality, being administered for six months or more after a low-dose challenge period." Even if studied from such a viewpoint, as stated above, it had already been administered on a yearly basis (10c). Moreover, due to such yearly administration, a person skilled in the art had not yet recognized the validity. However, there was also a report that life prognosis improved (10b). It can be said that there was some expectation regarding the improvement of the prognosis of life by adopting the administration period including the period of the annual unit " for six months or more after a dose escalation phase" as the administration period. It can be said that a person skilled in the art could easily conceive of adopting the administration form of "being administered for six months or more after a low-dose challenge period" for "decreasing mortality."

As stated above, in summary, based on common general technical knowledge before the priority date of the patented invention, a person skilled in the art could easily achieve "carvedilol being administered as a pharmaceutical agent for treating a patient with non-ischemic congestive heart failure having a symptom in class II or III, carvedilol being administered for at least three-month after a dose escalation phase" and "using as a pharmaceutical agent for decreasing mortality and administering the pharmaceutical agent for six months or more after a low-dose challenge period," which are stated in Exhibit A2. Thus, Invention 1 could have been easily invented by a person skilled in the art based on the invention stated in Exhibit A2 and common general technical knowledge before the priority date of the patented invention.

(3) Effect

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 with 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.

In addition, the demandee insists that "It realized the extremely remarkable effect of substantially decreasing mortality across both etiologies (ischemic and non-ischemic) and also substantially decreasing mortality across all classifications of CHF (all classifications from class II to IV)." However, as stated above, the statement "decreasing mortality ... substantially equally in ischemic and non-ischemic heart failure" in Invention 1 means that the administration of a pharmaceutical agent to patients with ischemic congestive heart failure and the administration of a pharmaceutical agent to patients with non-ischemic congestive heart failure are both included as aspects of Invention 1. Each aspect is interpreted to mean decreasing the mortality of patients. Among them, with respect to the effect on patients with non-ischemic congestive heart failure, a person skilled in the art could have predicted from Exhibit A2 and common general technical knowledge. Therefore, whatever the effect on patients with ischemic congestive heart failure, Invention 1 cannot be made to exert an unexpected effect as a whole.

This also applies to Invention 1 that similar descriptions are made regarding the severity as well as "decreasing mortality similarly in class III-IV symptoms."

(4) Other allegations of the demandee

The demandee insists that the inventive step of the present invention should be affirmed as follows by citing the statements of Exhibit A9 to A11. First, this matter will be examined.

(a) 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.

(b) 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.

(c) The statements of both Exhibits A9 and A11merely indicate the following: The survival rate of patients with heart failure was analyzed by stratifying the patients based on a specific ejection fraction value. As a result, the survival rate of the patient group exceeding the specific value was significantly higher than the survival rate of the patient group lowering the specific value. In other words, it does not indicate that, if a pharmaceutical agent that acts to increase the ejection fraction to patients with congestive heart failure, it can result in a decrease in mortality.

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

Regarding (a), 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 the symptoms of congestive heart failure were improved 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 (b), 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 matter of common general technical knowledge at 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 had been 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, it 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 (c), it is recognized that a procedure of dividing patients into a patient group that exceeds a specific ejection fraction value and a patient group that dips below the specific ejection fraction a specific value is merely a statistical procedure. However, such a fact itself cannot be a ground for denying that the ejection fraction affects the survival rate. In addition, Exhibit A15 relates to a pharmaceutical agent having a mechanism of action different from the β-blockers. Furthermore, Exhibit A 15 states that "it has been widely accepted that ACE inhibitors ameliorate the hemodynamics and symptoms of heart failure patients in the short term and long term and prolong the survival rate of the patients" (Exhibit A11, page 54, middle column, from the bottom, lines 7 to 4). Exhibit A15 also states that improvements in cardiac functions and symptoms of patients correlate with an improvement in life prognosis. Exhibit B18, published in the same year as the priority date of the patented invention, also states that the ejection fraction predicts the survival rate. In other words, "some parameters related to hemodynamics (e.g., ejection fraction) are excellent predictors for prognosis, but ..." (page 267, lines 33 to 34). The argument of the demandee concerning (c) cannot be accepted.

Next, in the written reply dated February 26, 2010, the demandee cites Exhibits B18 to 20 and alleges as follows:

(d) Exhibit B 18 states that, for example, "several parameters relating to hemodynamics (ejection fraction, cardiac index, wedge pressure, etc.) make the prognosis sufficiently predictable, but the correlation between other hemodynamic variables and prognosis is low or not established." (page 267, lines 33 to 35). In other words, it states that improvements in hemodynamics, etc., and a decrease in mortality are not correlated with each other and cannot be substituted for each other. The use in Invention 1 is clearly different from the use of carvedilol for "improving hemodynamic parameters and the like" stated in Exhibit A2.
(e) Exhibit B19 published before the priority date of the patented invention states that "only a doctor who had experience of using β-blockers for patients with heart failure permitted to use carvedilol with extreme caution." From the results stated in Exhibit A2, the hemodynamic parameters and the like only show improvement tendency. It was completely unknown whether carvedilol, which is a β-blocker, exacerbates or improve the mortality rate. It is not considered to be administered for more than four months.
(f) Referring the statement of Exhibit B20, the test results of the present specification allowed β-blockers including carvedilol to be positioned as class-II pharmaceutical agents and allowed β-blockers to be widely used as pharmaceutical agents for heart failure. This indicates that the findings obtained from the study of the present patent specification exceeded the prediction of a person skilled in the art.

These arguments cannot be the basis for affirming the inventive step of Invention 1 as well and will be stated as follows:

Regarding (d), the above consideration also presupposes that "treatment of congestive heart failure" in Exhibit A2 is based on the premise that it is different from that stated in Exhibit A2 is different from "an improvement in mortality of congestive heart failure" in Invention 1. Carvedilol, which is used for therapeutic application in Exhibit A2, can be easily used for improving mortality. Furthermore, Exhibit B18 states that "several parameters relating to hemodynamics (ejection fraction, cardiac index, wedge pressure, etc.) make the prognosis sufficiently predictable, but the correlation between other hemodynamic variables and prognosis is low or not established." However, the above consideration, it is not based on the assumption that the relationship between hemodynamic parameters and life prognosis is not necessarily established "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 a person skilled in the art difficult to recognize any conclusive evidence..." In addition, as a basis for facilitating the use of carvedilol, which is used for the therapeutic application stated in Exhibit A2. For improving the mortality rate, Exhibit B18 also states that Exhibit A2 includes a statement of improving parameters including ejection fraction, which is "to make the prognosis sufficiently predictable" (2b). According to the demandee's argument based on the statement of Exhibit B18, the above certification denying inventive step cannot be reversed.

Regarding (e), in common general technical knowledge before the priority date of the patented invention, which is the premise of the above consideration, "5-4-1. (C) Use of β-blockers in the treatment of congestive heart failure and the administration period thereof" states that (c-1) "β-blockers were previously contraindicated for cardiac failure, and the usefulness of β-blockers was not established in clinical practice. ... 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." In the above consideration, furthermore, there is a statement of "the administration of carvedilol being started at a very small dose .... and continued over a long period of time on the premise of careful observation ...". These are exactly the basis of consideration; on the assumption of the statement in Exhibit B19, "only a doctor who had experience of using β-blockers for patients with heart failure permitted to use carvedilol with extreme caution." Thus, (f) is not a basis for denying the above certification.

Regarding (f), based on the statement of "5-4-1." cited in the above (f), even if it was not necessarily established as of the priority date of the patented invention, a person skilled in the art could recognize that β-blockers would be effective as pharmaceutical agents when used under certain conditions. The demandee's allegation, which cited the statement of Exhibit B20 and stated that "according to the test results of the present specification, β-blockers to which carvedilol belongs have become members of the family of class-II pharmaceutical agents," merely indicates that β-blockers used under such certain conditions had subsequently been established as pharmaceutical agents. As a result, it is clear that Invention 1 cannot be regarded as one having a particularly unexpected effect.

The demandee also insists that Invention 1 should be recognized as a selection invention. However, as stated above, matters specifying the Invention could be easily made by a person skilled in the art. Thus, the effects of the Invention could be within the scope that could be predicted by a person skilled in the art. Accordingly, there is no room to interpret the Invention as a selection invention as the demandee insists.

5-4-2-3. Summary

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

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

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

Inventions 2 to 4 specify the administration protocol of carvedilol while referring to the statement of claim 1. Inventis 2 to 4 are as follows:

[Claim 2] The use of carvedilol as described in claim 1, wherein the use comprising administering to said patient 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.
[Claim 3] The use of carvedilol as described in claim 1, wherein the use comprises administering to said patient 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 12.5 mg.
[Claim 4] The use of carvedilol as described in claim 1, wherein the use comprises administering to said patient maintenance dosages once or twice daily, said maintenance dosages each comprising carvedilol in an amount of 25.0 mg or 50.0 mg.

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 twice. ... 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 to said patient 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 12.5 mg," is the 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 the 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 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 Week 3 of Invention 3, they overlap in terms of "administering to a pharmaceutical formulation containing 12.5 mg of carvedilol per dose unit twice a day for a period of 7 days."

The protocol of "administering to said patient 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 12.5 mg" stated in Invention 3 is the 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 of "finally administrating a pharmaceutical formulation that contains 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 they overlap in terms of "administrating a pharmaceutical formulation that contains 25.0-mg carvedilol per single unit as a maintenance dosage."

Thus, the protocol of "administering to said patient 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 12.5 mg" stated in Invention 4 is the 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, none of these inventions can 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, or any pharmaceutically acceptable salt 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, or any pharmaceutically acceptable salt 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 have been 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 have been easily made by a person skilled in the art. Furthermore, Invention 1 is an invention stated in Exhibit A2 and could have been easily invented by a person skilled in the art from the invention stated in Exhibit A2 and the technical common knowledge as of the priority date.

Consequently, Inventions 5 to 7 have 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 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 ischemic and non-ischemic congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV

symptoms, the pharmaceutical agent being administered for six months or more after a low-dose challenge period 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 for an additional period of 7 to 28 days, once or twice daily as a maintenance dosage."

5-4-5-2. Comparison/Examination

In the above "5-4-2. Regarding the Invention 1," just as comparison with Invention 1, Invention 8 will be now compared with the invention stated in Exhibit A2: "at least three-month administration of carvedilol after a dose escalation phase to patients with congestive heart failure due to idiopathic dilated cardiomyopathy, undergoing treatment with digoxin, furosemide, angiotensin converting enzyme ACE) inhibitor, the patient being in New York Heart Association (NYHA) Functional Class II or III, caused improvements in left ventricular systolic function at rest and maximal exercise, reduction in heart failure symptoms, and improvement in submaximal exercise tolerance."

The cited invention and Invention 8 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, wherein the use comprises administration of carvedilol alone or in combination with one or more of other pharmaceutical agents and cardiolol has the structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist" but are different from each other in the following points:

[Different feature 1] Invention 1 is read as "a pharmaceutical agent for decreasing mortality resulting from ischemic and non-ischemic congestive heart failure substantially equally in ischemic and non-ischemic congestive heart failure, and decreasing mortality similarly substantially in class III-IV symptoms, the pharmaceutical agent being administered for six months or more after a low-dose challenge period." In contrast, the invention stated in Exhibit A2 is read as "a pharmaceutical agent for treating a patient with non-ischemic congestive heart failure having a symptom in class II or III, the patient being given at least three-month administration after a dose escalation phase."

[Different feature 2] In Invention 8, the administration protocol is specified as follows, whereas such a specified feature is not made in the invention stated in Exhibit A2:

(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 7to 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 for an additional period of 7 to 28 days, once or twice daily as a maintenance dosage.

The above different feature 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 have been easily made by a person skilled in the art.

Then, different feature 2 will be examined.

As stated in "5-4-3. Regarding 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."
(see Exhibits A7, A8, and A10 ((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 make 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 a three-stage incremental application regimen including a three-stage application scheme, 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.

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 incremental administration 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 at the date of the Priority Claim of the Patent." (see Exhibits A7, A8, and A10 ((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 make 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 10 are inventions stated in Exhibit A2 and could have been easily invented by a person skilled in the art based on the invention stated in Exhibit A2 and a common general technical knowledge as of the priority date of the Patent. Any of Inventions 1 to 10 has been therefore 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.

Period.
March 29,2010

Chief administrative judge: HOSHINO, Shoei

Administrative judge: HIROZANE, Kenji
Administrative judge: TSUKANAKA, Tetsuo