Trial decision

Invalidation No. 2007-800192

Osaka, Japan Demandant	SAWAI PHARMACEUTICAL CO., LTD.
Tokyo, Japan Attorney	TAKAHASHI, Ryuji
Tokyo, Japan Attorney	SUGIMOTO, Shinsuke
Tokyo, Japan Attorney	SANO, Tatsumi
Tokyo, Japan Demandee	DAIICHISANKYO CO., LTD.
Tokyo, Japan Patent Attorney	KUMAKURA, Yoshio
Tokyo, Japan Patent Attorney	TSUJII, Koichi
Tokyo, Japan Patent Attorney	OGAWA, Nobuo
Tokyo, Japan Patent Attorney	HAKODA, Atsushi
Tokyo, Japan Patent Attorney	ASAI, Kenji
Tokyo, Japan Patent Attorney	HIRAYAMA, Koji
Tokyo, Japan Attorney	OKUMURA, Naoki
Tokyo, Japan Patent Attorney	TAKAISHI, Hideki
Tokyo, Japan Patent Attorney	SHINTANI, Masafumi

Regarding the Trial decision dated March 29, 2010 concerning the patent invalidation trial case of Patent No. 3546058 "Use of carbazole compounds for the treatment of congestive heart failure" between the parties, the Intellectual Property High Court made a decision of cancelling the trial decision (2010 (Gyo-Ke) 10140, rendering of decision on March 6, 2012), and as a result of further proceedings, a trial decision is made as follows.

Conclusion

The demand for trial of the case was groundless.

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

Reasons

No. 1 History of the procedures

The present application for the inventions according to claims 1 to 10 of the present patent No. 3546058 was filed on February 7, 1996 (Priority claim under the Paris Convention: February 8, 1995, Germany; June 7, 1995, USA) as an international filing date. Then, the establishment of the patent right was registered on April 16, 2004.

Against this, the demandant, Sawai Pharmaceutical Co., Ltd., demanded trial for patent invalidation of all the claims on September 13, 2007.

The history of subsequent procedures is as follows:

On March 3, 2008 a written reply and written correction request;
On August 14, 2008 an oral proceedings statement brief (demandee);
On August 19, 2008 an oral proceedings statement brief (demandant);
On August 27, 2008 oral proceedings;
On September 17, 2008 a change in indication of registered holder (from Boehringer Mannheim Pharmaceuticals Corporation-SmithKline Beecham Corporation Limited Partnership #1 to Boehringer Mannheim Pharmaceuticals Corporation-Smithkline Beckman Corporation Limited Partnership #1) and registration of transfer (to Roche Therapeutics Incorporated F. Hoffmann-La Roche Aktiengesellschaft and further, and then to Daiichi Sankyo Co., Ltd., thus, Daiichi Sankyo Co., Ltd.);
On September 19, 2008 a written statement (demandee);
On September 22, 2008 a written statement (demandant);
On October 27, 2008 a written statement (demandee);
On March 4, 2009 a trial decision (The correction shall be approved. The patent regarding to the inventions according to Claims 1 to 10 of Japanese Patent No. 3546058 shall be invalidated.);
On April 13, 2009 an action for revocation of trial decision (2009 (Gyo-Ke) 10101);
On May 12, 2009 a request for trial for correction (Correction 2009-390065);
On June 8, 2009 a court decision of revocation of the trial decision (Article 181(2) of the Patent Act);
On June 23, 2009 a written correction request (Article 134-3(2) of the Patent Act);

On August 4, 2009 a reply brief;
On February 26, 2010 a written statement (demandee);
On March 29, 2010 a trial decision (The correction shall be approved. The patent regarding to the inventions according to Claims 1 to 10 of Japanese Patent No. 3546058 shall be invalidated.);
On May 6, 2010 an action for revocation of trial decision (2010 (Gyo-Ke) 10140);
On June 2, 2010 a request for trial for correction (Correction 2010-390052);
On December 15, 2010 a trial decision for correction (The demand for trial of the case was groundless.)
On January 20, 2011 an action for revocation of trial decision (2011 (Gyo-Ke) 10018);
On November 30, 2011 a rendition of decision (2011 (Gyo-Ke) 10018: the trial decision on December 15, 2010 shall be rendered.)
On January 19, 2012, 2010 a trial decision for correction (The correction of the specification of Patent No. 3546058 shall be approved as the corrected specification attached to the written request for trial of the case.)
On March 6, 2012 a rendition of decision (2012 (Gyo-Ke) 10140: the trial decision on March 29, 2010 shall be rendered.)
On May 18, 2012 a notice of correction;
On June 14, 2012 a written opinion (demandant);
On June 26, 2012 a written statement (demandant);
On August 7, 2012 a notice of reasons for invalidation and notice of conclusion of trial proceedings
On September 3, 2012 a written opinion (demandant); and
On September 10, 2012 a written opinion (demandee).

No. 2 The Invention

The inventions according to claims 1 to 10 of the present patent No. 3546058 are those specified by matters stated in claims 1 to 10 of the scope of claims in the specification corrected by the trial for correction (Correction 2010-390052), as follows:

[Claim 1] Use of carvedilol in manufacture of a pharmaceutical agent for substantially similarly decreasing mortality in symptoms from Class II to IV resulting from ischemic 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 therapeutic agents, the pharmaceutical agent being administered for six months or longer with a low-dose carvedilol challenge period, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist,

<the structural formula is omitted>

wherein the therapeutic agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides.
[Claim 2] The use of carvedilol according to claim 1, wherein a pharmaceutical formulation that contains 3.125-mg or 6.25-mg of carvedilol per single unit is administered for a period of 7 to 28 days, once or twice daily as an initial dose.

[Claim 3] The use of carvedilol according to claim 1, wherein a pharmaceutical formulation that contains 12.5-mg of carvedilol per single unit is administered for a period of 7 to 28 days, once or twice daily.
[Claim 4] The use of carvedilol according to claim 1, wherein a pharmaceutical formulation that contains 25.0-mg or 50.0-mg of carvedilol per single unit is administered once or twice daily as a maintenance dose.
[Claim 5] The use of carvedilol according to claim 1, wherein the angiotensin converting enzyme inhibitors are selected from the group consisting of captopril, lisinopril, fosinopril, and enalapril, or any pharmaceutically acceptable salts thereof.
[Claim 6] The use of carvedilol according to claim 1, wherein the diuretics are selected from the group consisting of hydrochlorothiazide, torsemide, and furosemide, or any pharmaceutically acceptable salts thereof.
[Claim 7] The use of carvedilol according to claim 1, wherein the cardiac glycosides are selected from the group consisting of digoxin, β-methyldigoxin, and digitoxin.
[Claim 8] Use of carvedilol in manufacture of a pharmaceutical agent for substantially similarly decreasing mortality in symptoms from Class II to IV resulting from congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin, the pharmaceutical agent being administered for six months or longer with a low-dose carvedilol challenge period according to the regimen of:

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

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

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

[Claim 9] The use of carvedilol according to claim 8, comprising administering carvedilol in conjunction with one or more of other therapeutic agents, wherein the therapeutic agent is selected from angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides.
[Claim 10] The use of carvedilol according to claim 1 in preparation of a pharmaceutical agent for treatment of congestive heart failure adapted to be administered in a daily maintenance dose of 10 to 100 mg of carvedilol in an incremental dosage scheme including three application regimes:

a first regimen comprising administering 10% to 30% of the daily maintenance dose adapted to be administered for a period of 7 to 28 days; a second regimen comprising administering 20% to 70% of the daily maintenance dose adapted to be administered for an additional period of 7 to 28 days; and a third regimen starting after completion of the second regimen and comprising administering 100% of the daily maintenance dose.

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

No. 3 Outline of the demandant's allegation

The demandant demands the trial decision, "The patent regarding the inventions according to Claims 1 to 10 of Japanese 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 demandant alleges that the patent should be invalidated based on the following reasons:

(1) Since any of inventions of the respective claims 1 to 8 and 10 of the Patent is not the invention for which a patent is sought and is not stated in the detailed description of the invention, the Patent has been granted on a patent application not complying with the requirements prescribed in Article 36(6)(i) of the Patent Act and falls under Article 123(1)(iv) of the Patent Act, and should therefore be invalidated (hereinafter, referred to as "Reason for Invalidation 1").

(2) Since any of inventions of the respective claims 1 to 10 of the Patent is unclear as to which of the three invention categories (Article 2(3) of the Patent Act,) defined by the Patent Act it belongs, the Patent has been granted on a patent application not complying with the requirements prescribed in Article 36(6)(ii) of the Patent Act and falls under Article 123(1)(iv) of the Patent Act, and should therefore be invalidated (hereinafter, referred to as "Reason for Invalidation 2").

(3) If it is interpreted that the category of the Invention is an invention of process, the Invention (all claims) is an invention corresponding to a method for therapy or treatment of human diseases and does not correspond to "an invention that is industrially applicable" under the provisions of Article 29(1) of the Patent Act and falls under Article 123(1)(ii) of the Patent Act, and should therefore be invalidated (hereinafter, referred to as "Reason for Invalidation 3").

(4) Since the inventions of claims 1 to 10 of the Patent are substantially identical to the inventions stated in Exhibits A1 and A2 and falls under the provisions of Article 29(1) and also could be easily made by a person skilled in the art based on Exhibit A1 or A2 and should not be granted a patent under the provisions of Article 29(2) of the Patent Act, the Patent falls under Article 123(1)(ii) of the Patent Act and should therefore be invalidated (hereinafter, referred to as "Reason for Invalidation 4").

(5) Since the inventions of claims 1 to 10 of the Patent could be easily made by a person skilled in the art based on Exhibits A1 to A6, which were distributed prior to the filing of the Invention, the Patent should not be granted a patent under the provisions of Article 29(2) of the Patent Act, the Patent falls under Article 123(1)(ii) of the Patent Act and should therefore be invalidated (hereinafter, referred to as "Reason for Invalidation 5").

The evidence, etc. submitted by the demandant are as follows: (Note that some documents are represented with additional words by the body.)

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

Reference 1: "Introduction to Statistics in Medical Research", page 106, Table 7

Reference 2: "Clinical Trials 2003", page 19

<The above listed documents are attached to the written request for trial>

Exhibit A7: Today's Therapy 1993 (p5, pp 314-317)

Exhibit A8: Today's Therapy 1994 (p5, pp 312-313)

Exhibit A9: "Heart Failure - Recent Progress" in Cardiac Practice; (1990-7), vol. 1, No. 1, pp 17-23

Exhibit A10: "Heart Failure andβ-Receptor" in Cardiac Practice; (1990-7), vol. 1, No. 1, pp 25-32

Exhibit A11: "Prognosis of Heart Failure Patients" in Cardiac Practice; (1990-7), vol. 1, No. 1, pp 51-56

Exhibit A12: Section "Xamoteral" in The Merck Index, 14th Edition 2006

Reference 3: IFPMA Clinical Trial Portal HP

<The above listed documents are attached to the written request for trial dated September 22, 2008>

Exhibit A13: Medical Statistics Q&A, published October 30, 1987

Exhibit A14: Guidelines on Statistical Analysis of Clinical Trials, the Director General, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, March 4, 1992

Exhibit A15: Clinical Trials 2003, Yakuji Nippo Co. Ltd.

<The above listed documents are attached to the reply brief dated August 4, 2009>

Exhibit A16: The New England Journal of Medicine, vol. 334, No. 21, pp 1349-1355, (1996-5-23)

Exhibit A17: Circulation, vol. 94, No. 11, pp 2807-2816, (1996-12-1)

Exhibit A18: Circulation, vol. 94, No. 11, pp 2793-2799, (1996-12-1)

Exhibit A19: Circulation, vol. 94, No. 11, pp 2800-2806, (1996-12-1)

Exhibit A20: Journal of Cardiac Failure, vol. 3, No. 3, pp 173-179

Exhibit A21: The New England Journal of Medicine, vol. 335, No. 17, pp 1318-1325, (1996-10-24)

Exhibit A22: Heart, vol. 82 (Supplement IV) IV pp 14-22 (1999)

Exhibit A23: Invitation of comments on "Guideline on Clinical Evaluation of Antiepileptic Drugs" (November 16, 2009)

Exhibit A24: The LANCET, vol. 353, pp 9-13, (1999)

Exhibit A25: The LANCET, vol. 353, pp 2001-2007, (1999)

Exhibit A26: The New England Journal of Medicine, vol. 344, No. 22, pp 1651-1658, (2001-5-31)

<The above listed documents are attached to the written opinion dated June 14, 2012>

No. 4 Outline of the demandee's allegation

The demandee demands 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," and alleges that any of the demandant's allegations is groundless, submitting the following evidence:

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, vol. 8, pp 16-17, published June 30, 2005 by Life Science Co., Ltd.

Exhibit B7: Circulation, Vol. 103, No. 10 March 13, 2001; 1428-1433

Exhibit B8: Am. Heart J., Vol. 142, No. 3, 2001; 498-501

Exhibit B9: N. Engl. J.M ed., 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; 9 63-971

Exhibit B11: European Journal of Heart Failure, Vol. 9, 2007; 1128-1135

Reference 1: Written opinion dated March 10, 2003 (submitted by the applicant at the examination stage of the patent application)

<The above listed documents are attached to the written reply>

Exhibit B12: Today's Therapy 1992 (Volume 34), pp. 314-316, published on February 15, 1992

Exhibit B13: Today's Therapy 1995 (Volume 37), pp. 318-320, published on February 15, 1995

Exhibit B14: Today's Therapy 1996 (Volume 38), pp. 333-334, published on January 1, 1996

Exhibit B15: Today's Therapy 2008 pp. 288-293, published on January 1, 2008

<The above listed documents are attached to the oral proceedings statement brief>

Exhibit B16: Today's Therapy 1993 (volume 35) pp. 314-317, published on February 15, 1993

Exhibit B17: Today's Therapy 1994 (volume 36), pp. 312-313, published on February 15, 1994

<The above listed documents are attached to the written statement dated September 19, 2008>

Exhibit B18: Medical Products in the Treatment of Cardiac Failure, pp. 263-275, Nov., 1995

Exhibit B19: Clinical Practice Guideline (Number 11), Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic Dysfunction, "6 Pharmacological Management," pp. 49-66, June 1994

Exhibit B20: ACC/AHA Task Force Report, Guidelines for the Evaluation and Management of Heart Failure, "Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure), pp. 2764-2782, Nov., 1995

<The above listed documents are attached to the written statement dated February 26, 2010>

Exhibit B21: Written opinion dated September 8, 2010, created by Professor Toru Izumi of the Department of Cardiology, Kitasato University Hospital

Exhibit B22: Written opinion dated October 9, 2010, created by professor emeritus Hori Masashi of Osaka University

Exhibit B23: Written brief (1) dated March 10, 2011, submitted by the demandee in the IP high court (2011 (Gyo-Ke) 10018)

Exhibit B24: Written brief (2) dated March 10, 2011, submitted by the demandee in the IP high court (2011 (Gyo-Ke) 10018)

Exhibit B25: Description of evidence (2) dated March 10, 2011 and copies of Exhibits A13 to A52 submitted by the demandee in the IP high court (2011 (Gyo-Ke) 10018)

Exhibit B26: Written brief (3) dated June 30, 2011, submitted by the demandee in the IP high court (2011 (Gyo-Ke) 10018)

Exhibit B27: Written brief (4) dated August 5, 10, 2011, submitted by the demandee in the IP high court (2011 (Gyo-Ke) 10018)

Exhibit B28: Description of evidence (4) dated August 5, 2011 and copies of Exhibits A55 to A57 submitted by the demandee in the IP high court (2011 (Gyo-Ke) 10018)

<The above listed documents are attached to the written opinion dated September 10, 2012>

No. 5 Regarding Reasons for invalidation 1 to 3

1. Regarding Reason for invalidation 1

The demandant alleges that Inventions 1 to 8 and 10 are inventions including treatment by administration of carvedilol alone, the patent specification does not state the working effect of administration of carvedilol alone, and none of the above inventions is an invention for which a patent is sought, which is stated in the detailed description of the invention.

However, the allegation of the demandant cannot be accepted.

Invention 1 after the correction is as follows:

"Use of carvedilol in manufacture of a pharmaceutical agent for substantially similarly decreasing mortality in symptoms from Class II to IV resulting from ischemic 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 therapeutic agents, the pharmaceutical agent being administered for six months or longer with a low-dose carvedilol challenge period, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist, <the structural formula is omitted> wherein the therapeutic agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides."

On the other hand, in the detailed description of the invention in the patent specification, it is stated, "PBO (Placebo) or CRV (carvedilol) was added to existing therapy with digoxin, diuretics, and an ACE inhibitor." (publication of examined patent application, page 7, lines 9 to 10)

The use of carvedilol "alone" in Invention 1 means the administration of carvedilol alone for patients receiving current therapy with digoxin, diuretics, and ACE inhibitors. Thus, Invention 1 is one stated in the detailed description of the invention.

Since the invention according to claim 1 is stated in the detailed description of the invention, the inventions according to claims 2 to 7 and the inventions according to

claims 8 and 10, which are dependent on Claim 1, are stated in the detailed description of the invention.

Thus, the statement of the scope of claims of the patent specification cannot be regarded as failing to satisfying the provisions of Article 36(6)(i) of the Patent Act.

2. Regarding Reason for invalidation 2

The demandant alleges as follows: "use of carvedilol in manufacture of a pharmaceutical agent" in the Invention violates the provisions of Article 36(6)(ii) of the Patent Act because of its unknown category; and the Examination Guidelines stipulates that "use of substance X for the manufacture of a medicament for therapeutic --- " is interpreted as terms meaning "method for using substance X for the manufacture of a medicament for therapeutic --- ", but it is not clear whether it is the criterion applied in the combined use of medicaments.

However, the allegation of the demandant cannot be accepted.

The "manufactured pharmaceutical agent" in Invention 1 is "a pharmaceutical agent for substantially similarly decreasing mortality in symptoms from Class II to IV resulting from ischemic congestive heart failure in mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin, the pharmaceutical agent being administered for six months or longer with a low-dose carvedilol challenge period."

For administering multiple pharmaceutical agents, it is obvious that there is a case of a method of independently administering each of single agents separately containing their respective active ingredients and a method of administering a combination of agents each containing its active ingredient. Thus, the pharmaceutical agent may be assumed as a "single agent" including carvedilol only.

Furthermore, even if the agent is a single agent containing carvedilol or a combination of agents containing carvedilol, the use of carvedilol in manufacture can be interpreted as "a method for using" carvedilol in manufacture.

Thus, the invention according to claim 1 is "a method for using carvedilol for manufacturing pharmaceutical agent," or "a process invention." The invention according to claim 1 can therefore be clearly categorized, and thus the statement of claim 1 cannot be said to violate the provisions of Article 36(6)(ii) of the Patent Act.

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

3. Regarding Reason for invalidation 3

The demandant alleges that if the Invention is recognized as "an invention of process," it does not correspond to an invention that is industrially applicable because of being categorized in "methods of therapy of humans" and thus should not be granted a patent for the invention in accordance with the provisions of Article 29(1) of the Patent Act.

However, the Invention is an invention of use (method) of a substance (carvedilol) in manufacture of "a pharmaceutical agent" as described in claim and is thus apparently not an invention corresponding to a method of therapy of humans.

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

No. 6 Regarding Reasons for invalidation 4 and 5

As stated below, none of the allegations of the demandant can be accepted.

1. Regarding the allegation that the Invention is identical with the invention stated in Exhibit A1

(1) The following matters are stated in Exhibit A1, which is a publication distributed before the date of the Priority Claim of the patent application of the case (hereinafter, referred to as "the priority date for the Invention").
(Since the originally stated matters are in English, these matters are represented using the following translated text provided by the demandant. In this text, underlines in the text are added by the body.)

(1a) "Summary:

Several studies have demonstrated the long-term beneficial effects of beta-blockers in the treatment of congestive heart failure. Despite interest in this mode of therapy, clinical application of beta-blockers has been limited due to their negative inotropic effect. A subset of heart failure patients do not show improvements with standard beta-blocker therapy. Carvedilol, a new nonselective beta-blocking agent with concurrent alpha-blocking properties, was evaluated in 17 patients with chronic heart failure secondary to ischemic heart disease. All had resting left ventricular ejection fraction less than or equal to 45% and were maintained on diuretic therapy. Acute hemodynamic measurements were made after administration of intravenous carvedilol (2.5-7.5 mg) and after chronic therapy for 8 weeks (12.5 to 50 mg b.i.d.)". (page S62, Abstract, approximately lines 1 to 15)

(1b) "Patients

Patients entered into the study fulfilled the criteria of chronic CHF (congestive heart failure) for >6 months maintained on diuretics only and having previously suffered from at least one acute attack of left ventricular failure that required hospital admission, documented previous myocardial infarction (MI), New York Heart Association functional class II or III, (15), resting left ventricular ejection fraction of <45%, sinus rhythm on electrocardiography, and absence of acute myocardial ischemia based on lack of symptoms, exercise tests, and radionuclide imaging. The exclusion criteria for beta-blockers were applied and so patients of insulin dependent diabetes mellitus, chronic obstructive pulmonary disease, and peripheral vascular disease were excluded. Patients with blood pressure of more than 160/95 mmHg and those who had suffered a MI within 4 months were excluded." (page S63, left column, line 18 from the bottom to line 1 from the bottom)

(1c) "Study design

An uncontrolled, open-study design was used to evaluate the efficacy and safety of i.v. (2.5 to 7.5 mg) and oral carvedilol (12.5-50 mg twice daily). All cardioactive drugs other than diuretics were withdrawn at least 4 weeks before the study, and patients were maintained throughout the study on the same dosage of oral diuretics." (page S63, right column, lines 3 to 9)

(1d) "Result

The study group comprised 17 patients (11 men and six women; mean age, 68 years; age range, 50 to 78 years); all had suffered an MI in the past, and three patients had undergone coronary artery bypass graft surgery 3 to 6 years previously.

From 2.5 to 7.5 mg carvedilol i.v. was well tolerated by all of the patients, and no adverse events were recorded. None of the patients had evidence of pulmonary edema or severe hypotension that required intervention. Twelve of the 17 patients completed the 8-week chronic dosage period. Two patients suffered orthostatic hypotension after the first dose, one patient had worsening symptoms of heart failure, one developed unstable angina, and one patient died after sustaining an MI during the initial phase of study." (page S64, right column, lines 3 to 19)

(1e) "Response for long-term carvedilol therapy

Repeat hemodynamic measurements were made after 8 weeks of oral carvedilol therapy [data were published previously (22)]. In contrast to the acute i.v. response, there was a marked improvement of many of the hemodynamic parameters after chronic therapy with carvedilol. Mean systolic intra-arterial blood pressure, heart rate, pulmonary artery wedge pressure, right atrial pressure, and total systemic vascular resistance demonstrated significant reductions and were associated with concomitant symptomatic improvement in 11 of 12 patients. Although cardiac index did not change, there was a significant increase in mean stroke volume index after 8 weeks. Similarly, left ventricular ejection fraction increased significantly from basal values after chronic treatment, but only a small transient increase was noted after i.v. carvedilol." (page S64, right column, line 4 from the bottom to page S65, left column, line 14)

(1f) In summary, this preliminary study has demonstrated that a single i.v. dose of carvedilol was safe and well tolerated in the treatment of chronic heart failure of isochemic origin. The long-term benefit of oral carvedilol in the same patients far outweighs the limited efficacy of acute i.v. carvedilol, which may be attributed to reduction in oxygen demand, upregulation of sympathetic receptor activity in the myocardium, and vasodilation. Based on our previous data, recent studies of carvedilol in dilated cardiomyopathy have also shown similar beneficial effects in cardiac hemodynamics (30)." (page S66, right column, line 12 from the bottom to the last line)

According to the above statement, Exhibit A1 states that oral administration of carvedilol for 8 weeks to patients with ischemic congestive heart failure of classes II to III under treatment with diuretics (above 1b) leads to an improvement in hemodynamics parameter (above 1e). Thus, it is obvious that carvedilol (above 1a), which is a nonselective β-blocker having α-blocking effect, is used in manufacture of an orally administered preparation.

Therefore, Exhibit A1 states the following invention (hereinafter referred to as "Cited Invention").

"Use of carvedilol alone in manufacture of a pharmaceutical agent to be administered for 8 weeks, the pharmaceutical agent improving the hemodynamic parameters of patients with ischemic congestive heart failure in classes II to III receiving treatment with diuretics, wherein carvedilol is a nonselective β-blocker also having α-blocking activity by itself."

(2) Comparison

As drug therapy for congestive heart failure, it is well known to use vasodilators, such as diuretics and angiotensin converting enzyme inhibitors, and cardiotonic drugs, such as digoxin, alone or in combination therewith appropriately. (see, for example, Exhibit A7 and Exhibit A8)

Thus, "patients with ischemic congestive heart failure of classes II to III under treatment with diuretics" in the Cited Invention corresponds to "mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin" in Invention 1.

Carvedilol "a nonselective β-blocker also having α-blocking activity by itself" in Cited Invention has no difference from carvedilol "having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist" in Invention 1 <the structural formula is omitted>.

As stated above, as a drug therapy for congestive heart failure, it is well known to use vasodilators, such as diuretics and angiotensin converting enzyme inhibitors, and cardiotonic drugs, such as digoxin, alone or in combination therewith appropriately. In light of the technical significance, therefore, "use of carvedilol alone" in Cited Invention has no difference from "use of carvedilol alone or in conjunction with one or more of other therapeutic agents, ... wherein the therapeutic agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides" in Invention 1.

Comparing Invention 1 and the Cited Invention, therefore, corresponding and different features between them are as stated below.

[Corresponding features]

The corresponding features are "use of carvedilol in manufacture of a pharmaceutical agent administered to mammals undergoing background therapy with diuretics, angiotensin converting enzyme inhibitors, and/or digoxin, alone or in conjunction with one or more of other therapeutic agents, the pharmaceutical agent being administered for six months or longer with a low-dose carvedilol challenge period, the carvedilol having the following structure of both β-adrenoceptor antagonist and α1-adrenoceptor antagonist, <the structural formula is omitted> wherein the pharmaceutical agent is selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics, and cardiac glycosides."

[The different feature]

Invention 1 has a feature of "a pharmaceutical agent for substantially similarly decreasing mortality due to ischemic congestive heart failure in symptoms from Class II to IV, the pharmaceutical agent being administered for six months or longer with a low-dose carvedilol challenge period." In contrast, the Cited Invention has a feature of "a pharmaceutical agent to be administered for 8 weeks, the pharmaceutical agent improving the hemodynamic parameters of patients with ischemic congestive heart failure."

(3) Judgment by the body

Invention 1 and the Cited Invention are consistent in terms of their active ingredients (carvedilol), patients to be administered (patients with ischemic congestive

heart failure in classes II to III undergoing treatment with diuretics), and dosage regimen (10-mg to 50.0-mg administration once or twice daily, identified as 25.0 mg or 50.0 mg in Invention 4 depending on Invention 1). When the administration of carvedilol is continued for 6 months or more, it is obvious that the effect of lowering the mortality rate can be simultaneously attained even if carvedilol is administered for the purpose of improving the hemodynamic parameters of patients with ischemic congestive heart failure.

Then, the administration period in Cited Invention will be now considered.

Exhibit A1 is an article entitled "Can Intravenous β-blockade Predict Long-Term Hemodynamic Benefit in Chronic Congestive Heart Failure Secondary to Ischemic Heart Disease?" Exhibit A1 states that hemodynamics were compared between intravenous administration of carvedilol and continuation of oral administration thereof for 8 weeks, and mean stroke volume index and left ventricular ejection fraction were significantly improved as compared with before administration (above (1e)).

However, from the viewpoint of the object of study in Exhibit A1, it cannot be said that there is circumstance to be understood that the administration is expected to be further continued, for example, over a period of 6 months or more even after 8 weeks have elapsed.

Thus, the above difference cannot be regarded as a mere difference in expression, and Invention 1 cannot be regarded as being identical with the invention stated in Exhibit A1.

2. Regarding the allegation that Invention 1 is identical with the invention stated in Exhibit A2

The following matters are stated in Exhibit A2, which is a publication distributed before the priority date for the Invention and submitted by the demandant. (Since the originally stated matters are in English, these matters are represented using the following translated text provided by the demandant.)

(2a) "Conclusion. Short-term carvedilol administration reduces heart rate and mean pulmonary artery and pulmonary wedge pressures, whereas it improves both long-term rest and exercise left ventricular systolic function, reduces heart failure symptoms, and improves submaximal exercise tolerance in patients with idiopathic dilated cardiomyopathy." (page 1678, upper right column, lines 13 to 18)

(2b) In the first part of the study, the short-term hemodynamic effects of placebo or carvedilol (12.5 mg, orally) were evaluated on two successive days. ... After completion of the short-term phase of the study, patients resumed their usual dose of digitalis, diuretic drugs, angiotensin-converting enzyme inhibitors, and nitrates added to either placebo or carvedilol. Carvedilol was started at the dose of 6.25 mg twice daily with weekly increments to the doses of 6.25 mg three times a day, 12.5 mg twice a day, 12.5 mg three times a day, and, last, 25 mg twice a day. ... After the titration phase, patients continued to receive the maximal dose for at least 3 months." (page 1679, right column, line 22 from the bottom to page 1680, left column, line 5)

As stated above, in Exhibit A2, patients treated with carvedilol are not "patients with ischemic congestive heart failure" targeted by Invention 1 but "patients with idiopathic dilated cardiomyopathy."

Thus, Invention 1 cannot be regarded as being identical with the invention stated in Exhibit A2.

3. Regarding the allegation that Invention 1 could be easily made based on the invention stated in Exhibit A1 or the invention stated in Exhibit A2

As stated above, Exhibit A1 includes no statement about continuation of administration of carvedilol for 8 weeks or more.

Then, on the premise of upregulation of sympathetic receptor activity in the myocardium, long-term effects of improving hemodynamic parameters are inferred (above (1f)). In the publication distributed before the priority date for the Invention, the comparison between metoprolol and placebo (bogus medicine) indicates that an increase in β receptor concentration is caused by metoprolol (which is a β receptor blocker) but not by carvedilol (i.e., β-receptor upregulation does not occur).
(see Exhibit B2, page 27c, Figure 5 and page 28c, left column, lines 4 to 8)

Then, it is understood that a person skilled in the art could not anticipate whether similar effects can be obtained when the administration is continued for 8 weeks or more, for example, 6 months or more, from the effects of continuing administration of carvedilol for 8 weeks.

Moreover, at the time of the priority date for the Invention, it was contraindicated to use β-adrenergic receptor antagonists (β-blockers) for treatment of congestive heart failure. Even in the case of using some compounds, such as metoprolol, careful administration thereof is required. There was no established procedure of administration for congestive heart failure.
(see, for example, Exhibit A7, page 316, right column and Exhibit A8, page 313, left column)

Exhibit A1 states an example in which carvedilol, a β-adrenergic receptor antagonist, is administered for 8 weeks. However, for the purpose of improving hemodynamic parameters, it does not suggest the continuation of carvedilol administration for 8 weeks or more, for example, over 6 months.

Furthermore, in the invention stated in Exhibit A2, the patients who received carvedilol are not "patients with ischemic congestive heart failure" targeted by Invention 1 but "patients with idiopathic dilated cardiomyopathy."

Exhibit A2 states the continuation of carvedilol administration for at least 3 months, but lacks a statement about the continuation of carvedilol administration for 6 months or more as well as a statement about decreasing the mortality rate caused by congestive heart failure. (above (2a) and (2b))

Thus, it cannot be said that Invention 1 could be easily made based on the invention stated in Exhibit A1 or the invention stated in Exhibit A2.

4. Summary

As stated above, Invention 1 is not identical with the invention stated in Exhibit A1 or A2 and could not be easily made based on the invention stated in Exhibit A1 or A2.

Inventions 2 to 10 are inventions having all the matters specifying the Invention 1 and are further restricted by additional matters, and thus none of them is identical with the invention stated in Exhibit A1 or A2 and none could be easily made based on the invention stated in Exhibit A1 or A2 by the same reason.

5. Regarding Reason for Invalidation 5

(1) The demandant alleges that the Invention could be easily made by a person skilled in the art based on the inventions stated in Exhibits A1 to A6 distributed prior to the filing of the Invention.

As stated above, the Invention is not identical with the invention stated in Exhibit A1 or A2 and could not be easily made based on the invention stated in Exhibit A1 or A2.

Then, the matters stated in Exhibits A3 to A6 will be considered.

(2) The following matters are stated in Exhibits A3 to A6, respectively.

(3a) "The prevalence and mortality rate of heart failure increases with older people. The most important prognostic indicators are exercise tolerance and left ventricular function. Currently, medication therapy is composed of digitalis, diuretics, and ACE inhibitors. In future, drugs for controlling the extracardiac decompensation mechanism or novel surgical techniques for assisting or replacing the heart will be used." (Exhibit A3, page 172, Summary)

(4a) "A small amount of β-blocker is effective for some patients (resting tachycardia, proper blood pressure, and ambulatory patients) and may increase survival rate. In Australia and New Zealand, a large-scale trial of carvedilol (beta blocker with vasodilating effects) has been conducted for patients with mild to moderate heart failure due to ischemic heart disease. In the early stages of this study, we will observe the motor response and the effects on left ventricular size. If the result is good, a mortality trial will be conducted for 3000 patients."
(Exhibit A4, page 23, left column, lines 21 to 35)

(5a) In Exhibit A5, in Table 3 on page 196, trials are conducted from July 1992, in which the pharmaceutical agents are carvedilol versus placebo, for 18 months for exercise tolerance as preliminary, and 3 years for mortality, mainly. It is stated that 310 patients are participating under the current circumstances on July, 1993, and the scheduled completion date is 1996 or 1997.

(6a) "A β-blocker with a vasodilating action, such as carvedilol, suppresses the initial negative inotropic action due to the β-blocking action of the β-blocker. Thus, it may be particularly useful for heart failure. However, the negative inotropic action is particularly noticeable in the early stage of β-blockade. Thus, the administration of carvedilol should begin with only a small amount. If acceptable, carvedilol significantly improves functional, hemodynamic, and neurohormonal

parameters in long-term treatment." (Exhibit A6, page 90, left column, the section of 2.4 "Congestive heart failure")

(3) Judgment by the body

As stated in the above (4a) and (5a), the mortality trials with carvedilol have been carried out. However, no report has been made on a decrease in mortality rate as a result of the trials.

A small amount of β-blocker may cause an increase in survival rate of some patients (above (4a)), but no demonstrated possibility.

In addition, carvedilol is not just a β-blocker but also a compound having a vasodilating action. Moreover, as stated above, β-receptor upregulation behaves differently from other β-blockers. Thus, a potential for an increase in survival rate with β-blockers does not directly indicate that carvedilol has the effects of decreasing the mortality rate due to ischemic congestive heart failure. Thus, the effects of carvedilol to cause a decrease in mortality due to ischemic congestive heart failure cannot be inferred.

Furthermore, even though the items described in Exhibit A3 to A6 above are considered, the effects of carvedilol to cause a decrease in mortality due to ischemic congestive heart failure cannot be inferred.

The demandant presented References 1 and 2 and asserted as follows: "In clinical trials of medicines, the incidence rate of disease, changes in QOL, expression of side effects, etc. are called true endpoints as the evaluation items to be originally desired. However, it is difficult to observe and evaluate them in a short period of time. In general tests, therefore, clinical trials of pharmaceutical agents are conducted using surrogate endpoints (substitute endpoints) substituting for true endpoints as indicators. The true end point of heart failure disease is regarded as heart disease mortality rate, while the substitute end point is regarded as the left ventricular ejection fraction. In general, medicines are approved as substitute evaluation items. There are not a few cases where the effectiveness and safety of real endpoints are considered after approval. <omitted> It seems quite natural to confirm the validity and safety of medicines at the substitute endpoint by verifying the true endpoint."

However, considering Exhibits A3 to A6 do not clear the relationship between an increase in left ventricular ejection fraction and a decrease in mortality rate. Even if an increase in the left ventricular ejection fraction is obtained in Exhibit A1 (above (1e)), it cannot be inferred that the mortality rate will decrease immediately.

Thus, it cannot be said that Invention 1 could be easily made by a person skilled in the art based on the inventions stated in Exhibits A1 to A6.

6. Regarding other allegations of the demandant

(1) The demandant presented Exhibits A7 to A11 and alleged as follows: At the time of the priority date for the Invention, the usefulness of β-blockers in heart failure treatment had been established and improvements in exercise capacity, left ventricular ejection fraction, and so on were known to lead to an improvement in life prognosis, thereby allowing a person skilled in the art to predict the mortality rate in Invention 1. (Written statement dated September 22, 2008)

(A) Stated matters in Exhibits A7 to A11

Exhibit A7 states the following matters:

(7a) "β-blocker: Make an attempt in a case where normal antiarrhythmic drugs are not effective in cases where the functions are not improved or progressively deteriorated even with the treatment with the above pharmaceutical agents. Temporal deterioration of heart function may occur and it takes several months until its effect is developed.

Formulation Example

Metoprolol (Ropressol): Start dosing at 5 mg/day. Observe changes in the condition for about 2 months, and gradually increase unless cardiac function deterioration is noticed. Continue at 40 mg/day. Since there is no established administration method for congestive heart failure, case selection and increase in dosage are carefully carried out." (Exhibit A7, page 316, right column, line 14 from the bottom to line 5)

The following matters are stated in Exhibit A8.

(8a) "Recently, a widely accepted concept of cardiac dysfunction is that heart failure is accompanied with (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 patient symptoms and improving life, and (2) improving life prognosis." (page 312, right column, lines 5 to 10)

(8b) "e. β-blocker: In recent years, β-blocker therapy for dilated cardiomyopathy, which is important as an etiology of refractory heart failure, has attracted attention and its effectiveness is being confirmed. Future developments are therefore expected. However, in the past, β-blockers were pharmaceutical agents that were contraindicated for heart failure. In some cases, β-blockers worsen the symptoms and thus should be carefully administered." (Exhibit A8, page 313, left column, lines 7 to 12)

(8c) "β-blocker therapy for heart failure of dilated cardiomyopathy begins with a small amount and gradually increases. Long-term administration is required until its effect is developed.

11) Ropressol 5 mg for 2 min

In severe cases, 2.5 mg is a starting dose and is increased in increments of 5 to 10 mg at 1- to 2-week intervals, followed by a maintenance dose of 40 to 80 mg." (page 313, right column, lines 4 to 9)

The following matters are stated in Exhibit A9.

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

(9b) "The higher the death rate, the lower the left ventricular ejection fraction." (page 18, right column, lines 7 to 8)

(9c) "For improving the prognosis of heart failure, it is important how to stop lowering the contractility of the cardiac muscle and make it better if possible." (page 18, right column, lines 16 to 18)

(9d) "For this reason, attention has been given to β-blocker therapy that attempts to reduce the action of norepinephrine on the heart to cause β-receptor upregulation." (page 20, right column, lines 1 to 4)

The following matters are stated in Exhibit A10.

(10a) "1. Advantage/disadvantage of administration of β-blockers to heart failure

From 1975 to 1980, Sweden's group of Waagstein, Swedberg, et al. made a paradoxical series of reports that sympathetic β receptor blockers considered as being contraindicated for heart failure were administered to patients with severe dilated cardiomyopathy for a long time, and as a result exercise capacity, cardiac function, and prognosis of life were improved. Subsequently, several groups have confirmed that clinical improvement is observed in long-term administration of β-blockers in at least some dilated cardiomyopathy patients. Then, β-blocker therapy has come to be regarded as one of the leading treatments for chronic heart failure including dilated cardiomyopathy." (page 26, right column, line 4 from the bottom column to page 27, left column, line 5 from the bottom)

(10b) "A list of reports that the β-blockers were effective is shown in Table 1. On the other hand, a list of reports that the blockers were ineffective are summarized in Table 2. When comparing the two, in the ineffective reports, the blockers were administered for a short period, either in a single dose or at most within one month. On the other hand, in the reports that the blockers were effective, the blockers were administered for a long period, at most for several months or more. In many protocols, furthermore, the incremental administration of pharmaceutical agents was often carried out to the dose thereof to a maintenance dose of 25 to 100 mg/day. In these reports of administration for 3 months or more, improvements of cardiac functions, such as improvements of subjective symptoms and improvements of exercise capacity, left ventricular ejection fraction, left ventricular inner diameter, cardiac output, etc., were almost always recognized. Long-term administration of more than several months was considered necessary for the development of long-term effect. Furthermore, in the report of administration on a yearly basis, an improvement in life prognosis was recognized. In this study, however, only a small number of cases was examined. Thus, there is still room for further study on improvement of life prognosis." (page 27, left column, line 4 from the bottom to the same page, the middle column, last line)

(10c) "Selection and introduction of beta blockers

In order to reduce the risk of circulation failure at the time of introduction, it is important to start from a very small amount and then gradually increase the amount. It should be carefully increased in severe cases in which sympathetic nervous activity is accelerated remarkably. ... Metoprolol, which is the most reported, starts at 5 to 20 mg/day depending on the severity and is increased by the same amount every 1 to 2 weeks. Finally, patients often withstand the usual dose (metoprolol, 40-80 mg/day)." (page 31, left column, lines 1 to 16)

The following matters are stated in Exhibit A11.

(11a) "Heart failure is not a disease name but a symptomatic name. Thus, it elicits different opinions with respect to its clinically the most convenient definition. ... Cohn advocated the definition of heart function failure, which suits the present

conditions, as a concept of heart failure accompanied by (1) decreased exercise tolerance, (2) frequent occurrence of ventricular arrhythmia, and (3) decrease in survival rate.

Based on this definition, the purpose of treating heart failure will ultimately increase the survival rate of patients." (page 51, middle column, line 14 from the bottom to the last line)

(11b) "In 63 patients with dilated cardiomyopathy ... Schwartz, et. al. examined how significant the morphological findings and left ventricular hemodynamic index are in determining prognosis. During the observation period of 1124 days on average, 23 patients died. Patients with an ejection fraction of 35.5% or more showed a cumulative survival rate of 97% in the first year, 94% in the second year, and 85% in the fourth year. Less than 35.5% resulted in 71%, 44%, and 41% in the above respective years. According to multivariate analysis, this ejection fraction reduction allows prediction of survival rate with a significant difference of $p < 0.00001$." (page 52, left column, lines 7 to 19)

(11c) "Likoff, et al. followed up for 201 patients in total of patients with dilated cardiomyopathy and patients with ischemic cardiomyopathy for 28 months and investigated factors that affect mortality in heart failure patients. During this period, deaths of 85 patients were observed and among them 31% were sudden death. In this case as well, it was shown that survival rate was significantly different between patients with ejection fraction of 20% or more and those with ejection fraction of less than 20%." (page 52, left column, from the bottom, lines 10 to 3)

(11d) "Cohn et al. reanalyzed a famous clinical trial that revealed the function of a vasodilator called V-HeFT to cause a change in survival rates in patients with chronic heart failure, followed by study of various factors that affect prognosis. In clinical trials for the study, 642 patients were enrolled. Of these, 273 patients received placebo; 186 patients received combination therapy of hydralazine and isosorbide-dinitrate; and 183 patients received prazosin. <omitted> Hydralazine-nitrate reduced mortality by 28%, compared to the placebo group. No effect was observed with prazosin. <omitted> The average ejection fraction of all patients at the start of the trial was 28%. Thus, patients were divided into a group with values greater than 28% and a group with values equal to or lower than 28%. The mortality rate was significantly higher in the low ejection fraction group. In this group, furthermore, a more significant improvement in survival rate was observed by hydralazine-nitrate. Thus, the correlation between cardiac function and survival rate irrespective of the cause of heart failure suggests that the myocardial disorder itself causes poor prognosis." (page 52, left column, line 2 from the bottom to the same page, middle column, line 28)

(11e) After all, the ultimate goal of heart failure therapy is to increase the survival rate of patients. Factors that worsen prognosis include causal disease, left ventricular dysfunction, decreased exercise tolerance, blood catecholamines, arrhythmia, and the like. In starting treatment, it is necessary to have sufficient insight into its prognosis." (page 54, right column, from the bottom, lines 10 to 4)

(B) Judgment by the body

The demandant alleges that the usefulness of β-blockers in the treatment of heart failure had been established at the time of the priority date for the Invention.

However, based on the stated matter (above 7a) in Exhibit A7, the establishment of the usefulness can be denied.

Furthermore, the usefulness of β-blockers has been studied (above 8b to 8c, 9d, and 10a to c). The actions of β-blockers are due to β-blocker therapy trying to cause β-receptor upregulation (above 9d). As stated above, it is known that carvedilol does not cause β-receptor upregulation (see Exhibit B2, page 27c Figure 5 and page 28c, left column, lines 4 to 8). Thus, the effects of carvedilol cannot be predicted to be similar to those of β-blockers.

Next, the relationship between ejection fraction and mortality rate will be examined.

Exhibit A11 states that the mortality rate was significantly higher in the low ejection fraction group and a more significant improvement in survival rate by hydralazine-nitrate was attained. However, the statement does not clarify whether the ejection fraction was improved by hydralazine-nitrate, but reveals no effect with even with one of vasodilators, prazosin. (above 11d)

Then, it is clear that low ejection fraction in patients with chronic heart failure leads to an increase in mortality rate (above 9b and 11a to 11c). Even though reference is made to Exhibits A7 to A11, it is unknown whether the mortality rate decreases if the ejection fraction is improved by treatment and whether any pharmaceutical agent improves the ejection fraction.

Then, even though the ultimate goal of heart failure treatment is an increase in survival rate, or a decrease in mortality rate (above 11e), it should be said that a person skilled in the art could not predict a decrease in mortality rate of patients with congestive heart failure by use of carvedilol.

Even with reference to the stated matters in Exhibits A7 to A11, therefore, it cannot be said that Invention 1 could have been easily made by a person skilled in the art based on the invention stated in the publication distributed before the priority date for the Invention.

In addition, for the same reasons, it cannot be said that Inventions 2 to 10 could also have been easily made by a person skilled in the art based on the invention stated in the publication distributed before the priority date for the Invention.

(2) In the written opinion dated June 14, 2012 in response to the notice of correction, the demandant presents Exhibits A16 to A26 and alleges that the Invention has no effect of decreasing the mortality rate by 67% and exerts no significant effect.

(A) Outline of stated matters in Exhibits A16 to A26

Exhibits A16 to A20 are papers reporting in detail the results of the trials (US carvedilol trials) in the present specification. Exhibit A21 states the critical posts on the results of the US carvedilol trials, Exhibit A22 states that criticism of the main β-blocker mortality trials in chronic heart failure including the US carvedilol trials.

Exhibit A23 includes the statement pointing out that the number of cases in the clinical trial program, the settings of evaluation items, and so on were not appropriate for the test results on carvedilol (Exhibit A16).

Exhibit A 24 states that bisoprolol was assessed as causing a 34% reduction in mortality compared to placebo, and Exhibit A25 states that metoprolol was assessed as causing a 34% reduction in mortality.

Exhibit A26 states that carvedilol was assessed as causing a 35% reduction in mortality.

(B) Judgment by the body

Even though there is a problem in settings of conditions of the US carvedilol trials and there is a doubt that the value of mortality reduction effect in the present specification is 67% or 68%, it is clear from the statement of Exhibit A 26 that carvedilol has the effect of decreasing the mortality rate due to ischemic congestive heart failure.

Furthermore, at the time of the priority date, carvedilol had not been known to reduce the mortality caused by ischemic congestive heart failure. Thus, the US carvedilol trials were not designed to confirm a reduction in mortality, but were carried out without securing a sufficient number of patients to evaluate the mortality rate. The trials were discontinued due to confirming the advantageous effect compared with placebo (Exhibit A16, page 1350, right column, the first paragraph of "RESULTS").

Then, it cannot be said that the present invention has no remarkable effects in view of the state of the art at the time of the priority date of this case.

Next, the demandant alleges that the inventive step of the Invention should be denied because the effects of carvedilol in Exhibit A26 on mortality reduction are comparable with the effect of reducing mortality of bisoprolol and metoprolol in Exhibits A24 and A25.

However, all the mortality rates in Exhibits A24 and A25 were found after the priority date. Thus, the stated matters represent no technical level at the time of the priority date for the Invention.

Thus, the allegation of the demandant cannot be accepted.

No. 7 Closing

As stated above, from the reasons alleged by the demandant and evidence submitted thereby, the inventions according to claims 1 to 10 of the case cannot be invalidated.

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

October 31, 2012

Chief administrative judge: YOKOO, Shunichi
Administrative judge: FUCHINO, Ruka
Administrative judge: HIRAI, Hiroaki