Trial decision

Invalidation No. 2013-800139

Osaka, Japan Demandant	SAWAI PHARMACEUTICAL CO., LTD.
Tokyo, Japan Attorney	TAKAHASHI, Ryuji
Tokyo, Japan Attorney	IKUTA, Tetsuo
Tokyo, Japan Attorney	SANO, Tatsumi
Israel Intervenor	TEVA PHARMACEUTICAL INDUSTRIES LTD.
Tokyo, Japan Patent Attorney	JITSUHIRO, Shinya
Tokyo, Japan Attorney	NAGASAWA, Yukio
Tokyo, Japan Attorney	SASAMOTO, Setsu
USA Demandee	ELILILLYJAPANK.K.
Tokyo, Japan Patent Attorney	KOBAYASHI, Sumiko
Tokyo, Japan Attorney	KATAYAMA, Eiji
Tokyo, Japan Attorney	KURODA, Kaoru
Tokyo, Japan Patent Attorney	YOSHIMITSU, Maki
Tokyo, Japan Patent Attorney	HINO, Mami

The case of trial regarding the invalidation of Patent No. 2749247, entitled "Pharmaceutical formulations containing benzothiophenes" between the parties above has resulted in the following trial decision:

[Conclusion]

The correction shall be approved as requested.

The Patent on the invention according to claims 1 to 6 of Patent No. 2749247 was invalidated.

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

Reason

No. 1 History of the procedures

The application of the Patent regarding to the inventions of claims 1 to 6 in the scope of claims of Patent No. 274927 of the case (hereinafter, referred to as "the application for the Patent") was filed on July 28, 1993 as an international filing date (priority claim under the Paris Convention: July 28, 1992, United States (US)). For these inventions, the establishment of patent right was registered on February 20, 1998.

For this, the demandant filed a request for invalidation trial for the Patent on July 29, 2013 to invalidate the Patent for the inventions of claims 1 to 6. The demandee filed the written answer for trial on March 4, 2014. Then, in the first oral hearing conducted on June 26, 2014, the demandant made an oral statement to the trial examiner as described in the first oral proceeding record in accordance with the Oral Proceedings Statement Brief on June 12, 2014. The demandee made a statement as described in the same record in accordance with the Oral Proceedings Statement Brief on June 12, 2014. Furthermore, on July 10, 2014, the demandee filed the written statement. After that, an advance notice of a trial decision was notified on July 23, 2014. The demandee filed a written correction request and a written statement on October 27, 2014, and received a notice of reasons for rejecting a demand for correction on November 13, 2014. For this, the demandant filed a written opinion on January 8, 2015, while the demandee filed a written opinion on January 29, 2015 and then filed a written statement on February, 10, 2015.

A person applying to intervene submitted an application for intervention to the chief trial examiner (received on February 4, 2015). For this, the demandee filed a written opinion on March 16, 2015. Then, a decision on intervention was made on March 18, 2015 to permit the intervention of the person in the trial.

No. 2 Request for correction

According to the description of the written correction request, the object of request for correction and the contents of correction stated in the written correction request are as follows:

1. Object of request for correction

The request is made for correction on the specification of Patent No. 2749247 (hereinafter referred to as "the Description of the Patent") for each group of claims as stated in the corrected description attached to the written correction request.

2. Contents of correction
(1) Correction 1

In claim 1 of the scope of claims, the statement "a pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient." is corrected to the statement "a pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen."

(2) Correction 2

In claim 2 of the scope of claims, the statement "the pharmaceutical formulation of claim 1, wherein the active ingredient is raloxifene hydrochloride" is corrected to the statement "a pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the active ingredient of the pharmaceutical formulation is raloxifene hydrochloride, causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, as compared with tamoxifen."

3. Judgment of suitability of correction
(1) Regarding Correction 1

Correction to add the phrase "the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen" only means the addition of the obvious property of "a pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient."

In the Description of the Patent, paragraph 0076 of the Detailed Description of the Invention states as follows: "Increases in epithelial height are a sign of estrogenicity of therapeutic agents and may be associated with increased incidence of uterine cancer." and "At all doses given, tamoxifen increased epithelial height equal to that of an intact rat, about a six-fold increase over the response seen with raloxifene." In view of these statements, it can be said that the Detailed Description of the Invention explicitly states raloxifene as "the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen."

Thus, it can be said that Correction 1 is intended for clarification of ambiguous statement stipulated in Article 134-2(1) (iii) of the Patent Act.

Furthermore, Correction 1 is a correction within the scope of the matters stated in the description, the scope of claims, or the drawings attached to the application and does not substantially enlarge or alter the scope of claims. Therefore, Correction 1 complies with Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to the provisions of Article 134-2(9) of the Patent Act.

(2) Regarding Correction 2

In Correction 2, the correction to add the phrase "a pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising

raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient" to the statement of claim 1 falls under the dissolution of a citation relation between claims.

Next, the correction to add the phrase "causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, as compared with tamoxifen" only means the addition of the obvious property of "a pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient."

Then, in the Description of the Patent, paragraph 0076 of the Detailed Description of the Invention states as follows: "Increases in epithelial height are a sign of estrogenicity of therapeutic agents and may be associated with increased incidence of uterine cancer." and "At all doses given, tamoxifen increased epithelial height equal to that of an intact rat, about a six-fold increase over the response seen with raloxifene." In addition, paragraph 0077 of the Detailed Description of the Invention states as follows: "Estrogenicity was also assessed by evaluating the adverse response of eosinophil infiltration into the stromal layer of the uterus (Table 6). Raloxifene did not cause any increase in the number of eosinophils observed in the stromal layer of ovariectomized rats, while tamoxifen caused a significant increase in the response." In view of these statements, it can be said that the Detailed Description of the Invention explicitly states raloxifene as one "causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, as compared with tamoxifen."

Thus, it can be said that Correction 2 is to change the statement of claims dependent on other claims into claims that do not depend on other claims stipulated in Article 134-2(1)(iv) of the Patent Act, and is also intended for clarification of ambiguous statement stipulated in Article 134-2(1)(iii) of the Patent Act.

Furthermore, Correction 2 is a correction within the scope of the matters stated in the description, the scope of claims, or the drawings attached to the application and does not substantially enlarge or alter the scope of claims. Therefore, Correction 2 complies with Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to the provisions of Article 134-2(9) of the Patent Act.

As stated above, the correction of the case is intended for the matters listed in any of the items of Article 134-2(1)(iii) and (iv) of the Patent Act, and thus complies with Article 126(5) and (6) of the Patent Act as applied mutatis mutandis pursuant to the provisions of Article 134-2(9) of the Patent Act.

Therefore, the Correction of the case shall be approved.

No. 3 Corrected invention of the case

The inventions of claims 1 to 6 in the scope of claims of Patent No. 2749247 of the case (hereinafter, referred to as "Corrected Invention 1" to "Corrected Invention 6" in this order and collectively referred to as "Corrected Invention") can be recognized as those specified by the matters stated in the scope of claims in the corrected description attached to a written correction request on October 27, 2014, as follows:

"[Claim 1] A pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen.
[Claim 2] A pharmaceutical formulation for treating or preventing human osteoporosis, the formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the active ingredient of the pharmaceutical formulation is raloxifene hydrochloride, causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, as compared with tamoxifen.
[Claim 3] The pharmaceutical formulation of claim 2, wherein the formulation is prepared for administration of raloxifene hydrochloride at 50 to 200 mg/day.
[Claim 4] The pharmaceutical formulation of claim 1, wherein the formulation is in unit dosage form containing 50 to 200 mg of the active ingredient.
[Claim 5] The pharmaceutical formulation of claim 4, wherein the active ingredient is raloxifene hydrochloride.
[Claim 6] The pharmaceutical formulation of claim 4, wherein the unit dosage form is prepared for oral administration."

No. 4 Allegations of the parties and means of proof submitted by the parties

1. Reasons for invalidation alleged by the demandant and the means of proof submitted by the demandant

The demandant demands the decision, "The Patent for the inventions of claims 1 to 6 of Patent No. 2749247 shall be invalidated. The costs in connection with the trial shall be borne by the demandee." For that reason, the demandant alleged the reasons for invalidation below, and submitted Exhibits A1 to A14 and References 1 and 2 as means for proof.

(1) Reason for invalidation

The inventions according to claims 1 to 6 of the Patent could be provided easily by a person skilled in the art according to Exhibits A1 and Exhibits A2 to A4 prior to the application. The Patent for the inventions 1 to 6 according to claims 1 to 6 of the present case violates the provision of Article 29(2) of the Patent Act and should be invalidated.

(2) Means of proof
Exhibit A1: Breast Cancer Research and Treatment, Vol. 10, pp. 31-35, 1987
Exhibit A2: Journal of the National Cancer Institute, vol. 81(14), pp. 1086-1088, 1989
Exhibit A3: Japanese Unexamined Patent Application Publication No. S57-181081
Exhibit A4: Oncology Vol. 45, pp. 344-345, 1988
Reference 1: European Patent No. 1438957
Reference 2: decision on opposition on December 22, 2009 to the grant of European Patent No. 1438957

(these are attached to the written demand for trial)

Exhibit A5: Japanese Unexamined Patent Application Publication No. S57-181081
Exhibit A6: Life Sciences, Vol. 32, pp. 2869-2875 (1983)
Exhibit A7: Cancer Research, Vol. 47, pp. 4020-4024 (1987)
Exhibit A8: Life Sciences, Vol. 32, pp. 1031-1036 (1983)
Exhibit A9: The written oath of V. Craig Jordan (author of Exhibit A1) on September 19, 2012
Exhibit A10: Document search result by literature database Scopus
Exhibit A11: Black et al., J. Clin. Invest. 93:63-69 (1994)
Exhibit A12: The written oath of Dr. Jan Urban Lindgrenon on October 7, 2009
Exhibit A13: The written oath of Dr. Joharm Diederich Ringe on October 7, 2009
Exhibit A14: List of reference numbers of evidences in opposition to the corresponding European patent

(these are attached to the Oral Proceedings Statement Brief)

2. Allegations of the demandee and means of proof submitted by the demandee

The demandee demands the decision, "The demand for trial of the case was groundless. The costs in connection with the trial shall be borne by the demandant." For that reason, the demandee alleges that no invalidation reason exists and then files Exhibits B1 to B25 as means for proof.

(1) Means of proof
Exhibit B1: Sone, Transactions of the Japanese Society for Medical and Biological Engineering 44(4): 511-516, 2006
Exhibit B2: Wronski and Yen, Cells, and Materials, Supp. 1: 69-74, (1991)
Exhibit B3: Kiminel, et al., Calcified Tissue International (1990) 46: 101-110
Exhibit B4: The written expert's opinion of Dr. Scott Miller
Exhibit B5: Larry Black, Certificate of experimental results
Exhibit B6: Draper et al., Fourth International Symposium on Osteoporosis, Hong Kong, 1993, pp. 119-121
Exhibit B7: Fukai, Journal of Okayama Medical Association, 71(8-1), 4881-4888, 1959-08-10
Exhibit B8: Miller et al., Calcified Tissue International (1982)34:245-252
Exhibit B9: Calcified Tissue International, 35(6), Sept. 1983. Instructions to Authors
Exhibit B10: Williain John Huster, "Reanalysis of data found in articles of Jordan, Phelps, and Ringlen"
Exhibit B11: Malfetano, Gynaecological Oncology 39, 82-87, 1990
Exhibit B12: Spinelli, J. Chemotherapy, 3(4), 267-270, 1991
Exhibit B13: Fornander, Lancet, 117-120, 1989
Exhibit B14: Jordan, Lancet, 733-734, 1989
Exhibit B15: Gal et al., Gynaecological Oncology 42, 120-123, 1991
Exhibit B16: Feldmann et al., Bone and Mineral 7:245-54 (1989)
Exhibit B17: Chander et al., Cancer Res 1991 51 5851-5858
Exhibit B18: Lindstrom et al., Xenobiotica 14 (11) pp. 841-847 (1984)

(These are attached to the written answer for trial.)

Exhibit B19: Takayoshi Onodera and Yutaka Hisimura, "New statistical studies for literary students" pp. 71-73, 2005, Nakanishiya Shuppan

(These are attached to the Oral Proceedings Statement Brief.)

Exhibit B20: Miller, S.C. et al., Bone 7: 283-287, 1986
Exhibit B21: Marcus, R. et. al., Ed., Osteoporosis, pp. 671-690, Academic Press, 1996
Exhibit B22: Marcus, R. et al., Ed., Osteoporosis (4th Ed.), pp. 939-961, Academic Press, 2013

(These are attached to the written statement on October 27, 2014)

Exhibit B23: "Guidelines for Prevention and Treatment of. Osteoporosis. 2011 Edition" pp. 2-3 (Life Science Publishing)
Exhibit B24: Marcus, Trends Endcrinol Metab 1991. 2. 53-58
Exhibit B25: Addition of the abstract of Exhibit B2

(These are attached to the written statement on February 10, 2015.)

No. 5 Judgment by the body

The body judged that the Patent for Corrected Inventions 1 to 6 should be invalidated due to the above reasons for invalidation. The reasons are as follows.

1. Statement in Exhibit A

Exhibit A1 states as follows: (Exhibit A1 is described in English, and thus translated in Japanese)

(A) (page 31, summary, lines 1 to 9)

The effects of the antiestrogens tamoxifen and keoxifene on the bone density of intact and ovariectomized female rats were determined after 4 months of therapy. The antiestrogens did not cause a decrease in bone density in intact animals, although uterine wet weight did decrease. Ovariectomy caused an increase in body weight (25%) and a significant decrease in femur density ($P<0.01$). Antiestrogens did not further decrease the bone density of ovariectomized rats but rather helped to maintain bone density. Antiestrogens as well as estrogen (oral estradiol benzoate ester 25 μg daily) helped to maintain bone density in the range observed for the intact rats, but inhibited estrogen stimulation of uterine weight. These contrasting pharmacological actions of antiestrogens suggest that patients receiving long-term adjuvant tamoxifen therapy for breast cancer should be evaluated to determine whether tamoxifen can retard the development of osteoporosis.

(B) (page 31, right column, lines 1 to 4)

A recent report demonstrated that the antiestrogen clomiphene could actually protect ovariectomized rats from a decrease in bone density [10].

(C) (page 31, right column, line 12 to the last line)

In this study, we have focused our attention on tamoxifen, a pure trans isomer of a substituted triphenylethylene related to clomiphene [1], and keoxifene, an

antiestrogen with a high affinity for the estrogen receptor but weaker estrogenic properties than tamoxifen [12]. These antiestrogens have been studied to determine their effects upon intact or ovariectomized rat bone density.

(D) (page 32, left column, lines 7 to 10)

Keoxifene (6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thiene-3-yl-4-[2-(1-piperidine) ethoxyphenyl] methane hydrochloride) was obtained from Eli Lilly Laboratories, Indianapolis, IN.

(E) (page 32, left column, lines 13 to 30)

Seventy-nine 9-month-old retired, female breeder rats were randomly allocated to 10 treatment groups. Seven rats were used as baseline controls, and the remaining animals were either ovariectomized or underwent a sham operation. Rats were treated daily (per os in 0.2 ml peanut oil) with tamoxifen (100 μg), keoxifene (100 μg), or estradiol-3-benzoate ester (25 μg), or with a combination of either tamoxifen or keoxifene and estradiol-3-benzoate ester. These doses were selected based upon their known pharmacology [1] and prior experiments with these compounds in this laboratory [1, 13]. One group of eight ovariectomized and eight sham-operated rats received only the vehicle. The experiment was continued for four months. All rats were housed in individual cages, and received distilled water and a laboratory diet of 0.5% Ca and 0.3% P *ad libitum* [14].

(F) (page 32, left column, the last line to right column, line 17)

The rats were killed by exsanguination under pentobarbital anesthesia. The femurs were harvested and immediately frozen; later they were thawed and dissected from the soft tissues. The length of the femur and the mid-diaphyseal width were measured. The bones were put in distilled water for 6 hours, then weighed in distilled water and took out of distilled water. The difference between these measurements, expressed in grams, equals the bone volume in cubic centimeters. Fat and water were removed from the bones with six 48-hours changes of acetone. The bones were dried at 50°C for 24 hours, and their dry weights were recorded. Then the bones were put in a 500°C furnace for 48 hours and reduced to ash. The ash weight was then determined with standard procedures. Statistical comparisons were (when indicated) made with Student's t-test.

(G) (page 32, right column, lines 21 to 26)

There was a significant decrease in bone density when these 9-month-old rats were ovariectomized. After 4 months, the mean dry weight and total ash of the femur were significantly lower for the ovariectomized rats compared to the intact controls (Table 1).

(H) (page 32, Table 1)

Table 1. Effects of ovariectomy in old rats after four months. Results are mean ± standard deviations. Eight per group.

13-Month-old-rats	Body weight (g)	Dry weight of femurs (g)	Total ash of femurs (g)	Ash/Volume of femur (g/cm^3)
Normal	306 ± 25 b	0.608 ± 0.041 c	0.404 ± 0.028 c	0.703 ± 0.034 c
Ovariectomized	351 ± 42 c	0.535 ± 0.045 a	0.349 ± 0.026 a	0.618 ± 0.038 b
(Baseline	259 ± 20	0.492 ± 0.040	0.315 ± 0.027	0.664 ± 0.024)

Probability of no difference between groups:
a 0.05>P>0.01
b 0.01>P>0.001
c P<0.001.

(I) (page 34, left column, lines 2 to 6)

Estradiol benzoate esters doubled the uterine wet weight of ovariectomized rats, whereas tamoxifen and kaoxifen only slightly increased uterine wet weight (Fig. 2).

(J) (page 33, Figure 2)

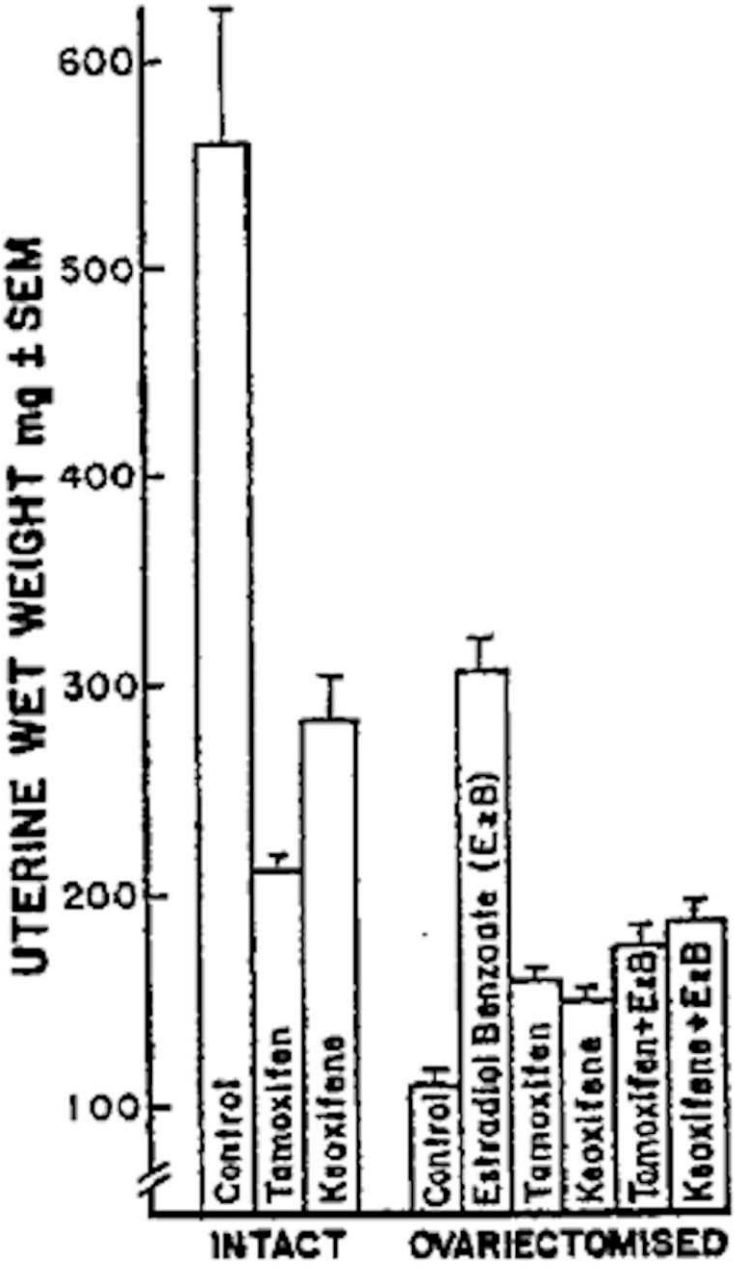

Fig. 2. The effect of four months of treatment with antiestrogens or estrogen (estradiol benzoate ester E2B) to intact or ovariectomized rats (8 per group) on uterine wet weights. See Materials and methods for treatment regimens.

(K) (page 34, left column, lines 12 to 19)

Estradiol benzoate ester slowed a decrease in ash density caused by ovariectomy, but it was not statistically significant. In contrast, both tamoxifen and keoxifene significantly delayed a decrease in ash density caused by ovariectomy ($p < 0.05$). Then, the combination of estradiol benzoate ester and antiestrogens had at least an equivalent effect. Indeed, the combination of estradiol and antiestrogens was not

significantly different from each intact control group administered antiestrogen alone (Fig. 3).

(L) (page 33, Fig. 3)

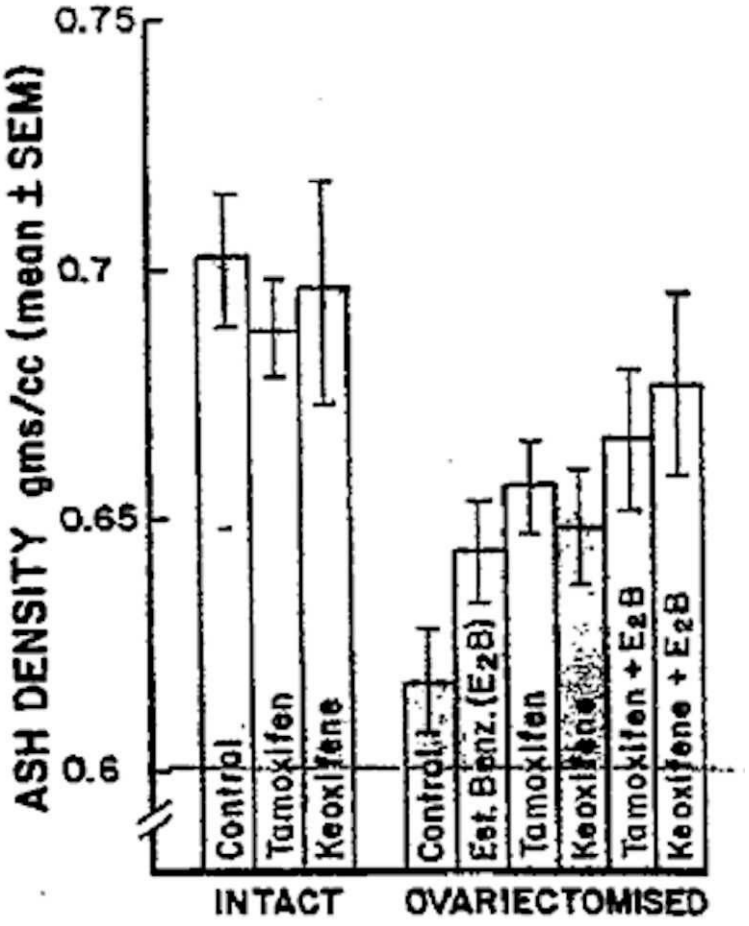

Fig. 3. The effect of four months of treatment with antiestrogens or estrogen (estradiol benzoate ester E2B) to intact or ovariectomized rats (8 per group) on femur ash density. See Materials and methods for treatment regimens.

(M) (page 34, left column, from the bottom, line 4 to right column, line 4)

Consideration

This study was designed to confirm the effects of antiestrogen and/or ovariectomy on the bone density of elderly rats. As mentioned earlier [14, 15], elderly rats showed osteoporotic changes with ovariectomy. However, a pharmacologically active oral dosage of antiestrogen did not alter the bone density of intact rats.

(N) (page 34, right column, lines 14 to 26)

Estrogen can restore osteoporosis occurring in female rats [18]; we chose low-dose estradiol benzoate ester that could control the observed weight gain in ovariectomy. Anti-estrogen stabilizes bone loss in ovariectomized rats. Surprisingly, in combination of antiestrogen and estradiol, bone density was substantially maintained

at the level of intact rats. The results show complete inhibition of uterine wet weight by estrogen stimulation and show target site specificity of antiestrogen together with positive estrogen-like effects on both weight and bone density.

2. Judgment
(1) Regarding Corrected Invention 1

According to Described matter (A), (B), (C), and (M), since antiestrogen clomiphene was known to be able to prevent a decrease in bone density of ovariectomized rats, Exhibit A1 is a document that focused on antiestrogen keoxifene and disclosed a study conducted aiming at confirming the effects of keoxifene on the bone density of elderly ovariectomized rats.

As stated in Described matters (E) and (F), 9-month-old retired, female breeder rats were ovariectomized and orally treated with keoxifene (100 μg) daily for 4 months. The rats were sacrificed and then the length of the femur and the width of the medial diaphysis were measured. Bone volume, dry weight, and ash density were also measured. Statistical comparison was made by Student's t-test.

According to the Described matters (G) and (H), a significant decrease in bone density was observed when 9-month rats were ovariectomized.

By summing up all these statements, Exhibit A1 is recognized as one that states the invention (hereinafter referred to as "Cited Invention") as follows:

"Antiestrogen keoxifene is characterized in that 9-month-old retired, ovariectomized female breeder rats were orally treated with keoxifene (100 μg) daily for 4 months for the purpose of confirming the effects of keoxifene on the bone density of elderly ovariectomized rats, and as a result a decrease in ash density due to ovariectomy was delayed significantly."

Then, Corrected Invention 1 is compared with Cited Invention.

"Raloxifene" of Corrected Invention 1 is a compound represented by "6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thiene-3-yl-4-[2-(1-piperidine) ethoxyphenyl] methane." On the other hand, according to Described matter (D), "keoxifene" of Cited Invention is a compound represented by "(6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thiene-3-yl-4-[2-(1-piperidine) ethoxyphenyl] methane hydrochloride)." The name of the compound representing "raloxifene" of Corrected Invention 1 is "--- methanone," whereas the name of the compound representing "keoxifene" of Cited Invention is "--- methane hydrochloride." Thus, these compounds appear to be different. However, it is obvious to a person skilled in the art that raloxifene and keoxifene mean the same compound (if necessary, refer to THE MERCK INDEX THIRTEENTH EDITION, MERCKCO., INC. 2001, p. 1452, the item "8190. Raloxifene"). "--- methane hydrochloride" of Described matter (D) of Exhibit A1 is error of "--- methane hydrochloride" and "keoxifene" of Cited Invention is recognized as hydrochloride of raloxifene of Corrected Invention 1

Next, keoxifene of Cited Invention is used for "oral treatment." Usually, in oral treatment, it is common to use it as a formulation of some kind. In addition, it is clear that "antiestrogen keoxifene" is a medicine. Thus, it can be said that "antiestorogen keoxifene" is "a pharmaceutical formulation comprising raloxifene as an active ingredient."

Corrected Invention 1 and Cited Invention are identical in terms of "a pharmaceutical formulation comprising raloxifene or a pharmaceutical salt thereof as an active ingredient" but at least literally different from each other in terms of the following features:

- Corrected Invention 1 is "for treating or preventing human osteoporosis," while Cited Invention is characterized in that "9-month-old retired, ovariectomized female breeder rats were orally treated with raloxifene (100 μg) daily for 4 months for the purpose of confirming the effects of raloxifene on the bone density of elderly ovariectomized rats, and as a result a decrease in ash density due to ovariectomy was delayed significantly." (hereinafter, referred to as "Different feature 1").

- Corrected Invention 1 states that "the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen" but Cited Invention does not include such a statement (hereinafter, referred to as "Different feature 2").

Therefore, the above different features will be examined.

(a) Regarding Different feature 1

In Described matter (M) of Exhibit A1 states that "elderly rats showed osteoporotic changes with ovariectomy." Thus, it can be said that "elderly ovariectomized rats" and "9-month-old retired, ovariectomized female breeder rats" in Cited Invention are rats that showed osteoporotic changes.

Furthermore, in Described matter (A), there is a statement that "These contrasting pharmacological actions of antiestrogens suggest that patients --- should be evaluated ---." In view of such a statement, it is recognized that a person skilled in the art who touches Exhibit A1 recognizes Exhibit A1 as a document reflecting the knowledge obtained in rats in humans.

(b) Furthermore, Exhibit B2 (page 69, left column, lines 2 to 5) states that "many similarities between rats and humans in bone response to estrogen deficiency are the basis for using ovariectomized rats as an animal model of postmenopausal bone loss." Thus, the fact that "ovariectomized rats" are "an animal model of human postmenopausal osteoporosis" was a matter of technical common sense at the priority date of the Patent.

(c) Next, the term "bone density" and "ash density" referred in Cited Invention are not defined in Exhibit A1.

In further examination of the description of Exhibit A1, Described matter (G) states that "significant decrease in bone density when these 9 month old rats were ovariectomized," while Described matter (K) states that "a decrease in ash density

caused by ovariectomy." Both described matters state the phenomena that occurred in the bones after rat ovariectomy. Thus, a person skilled in the art who touched on these statements could recognize that the terms "bone density" and "ash density" refer to the same meaning of density. In addition, the terms can be recognized as densities calculated by "Ash/Volume of femur (g/cm^3)" in Table 1 of Described matter (H) in which a concrete method of calculation for a density is described only in Exhibit A1.

(d) According to (c), "a decrease in ash density due to ovariectomy was delayed significantly" in Cited Invention can be rephrased as "a decrease in ash density due to ovariectomy was delayed significantly." Then, in Exhibit A1, it is recognized that a change in bone density and a change in osteoporosis correspond with each other as stated in Described matter (M), "elderly rats showed osteoporotic changes with ovariectomy. However, a pharmacologically active oral dosage of antiestrogen did not alter the bone density of intact rats."

(e) By summing up all these statements, Exhibit A1 may state that raloxifene of Cited Invention has an effect of delaying the onset and progression of osteoporosis in ovariectomized rats, which are an animal model of human postmenopausal osteoporosis.

Then, in ovariectomized rats, which are an animal model of human postmenopausal osteoporosis, raloxifene has an effect of delaying the onset and progression of osteoporosis. Thus, according to Cited Invention, a person skilled in the art could easily conceive of applying "a pharmaceutical formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient" to the treatment or prevention of human osteoporosis.

(f) Regarding Different feature 2

Regarding the statement "the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen" in Corrected Invention 1, even considering the description of the Detailed Description of the Invention, there is no mention that the dosage and administration of "a pharmaceutical formulation comprising raloxifene or a pharmaceutical acceptable salt thereof as an active ingredient," additives, etc. were examined in order to satisfy the condition "the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen."

Thus, the above statement "the pharmaceutical formulation has lower risk of uterine cancer than tamoxifen" can be recognized as one that merely states the inherent properties of "a pharmaceutical formulation comprising raloxifene or a pharmaceutical acceptable salt thereof as an active ingredient." It can be also recognized that such inherent properties of the pharmaceutical formulation can be those naturally imparted to a pharmaceutical formulation comprising raloxifene of Cited Invention as an active ingredient.

In this respect, therefore, it cannot be said that Corrected Invention 1 is an invention different from Cited Invention.

(g) Next, considering the effect, as discussed above, raloxifene is predicted to be effective in treating or preventing human osteoporosis.

Furthermore, Described matter (N) of Exhibit A1 states that antiestrogen; i.e., raloxifene, has target site specificity. In addition, Described matters (I) and (J) state that raloxifene only slightly increased the uterine wet weight of ovariectomized rats. Thus, a person skilled in the art could easily predict that raloxifene does not show uniform action in the body, raloxifene has the effect of delaying a decrease in bone density in the bones, and raloxifene shows little proliferative action in the uterus.

(h) In the written answer, the Oral Proceedings Statement Brief, the written statement on July 10, 2014, the written statement on October 27, 2014, and the written statement on February 10, 2015, on the basis of the reasons (h-1) to (h-5) stated below, the demandee alleges that the technical matter "a decrease in bone density due to rat ovariectomy was significantly delayed by raloxifene" cannot be found in Exhibit A1.

(h-1) In the retired breeding rats, ovariectomy did not show a decrease in bone density

"Retired breeding rats differ significantly in important bone parameters among individuals .... It is impossible to properly compare treatment group and non-administration group" (the written answer 18 page, lines 21 to 25)

"In fact, when using retired breeding rats, no data was obtained to prove a decrease in bone density due to ovariectomy. Thus, we verified that the use of retired breeding rats cannot obtain a model that reliably reproduces human osteoporosis." (the written answer, page 18, line 26 to page 19, line 2)

(h-2) The ash density measured in Exhibit A1 is unrelated to bone density for the evaluation of osteoporosis.

"In rats, the period during which the cortical bone continues to grow is long. On the other hand, in humans, it is known that --- especially in women close to menopause as well as postmenopausal women, --- bones never grow." (the written answer, page 20, lines 5 to 8)

"The data of ash density shown in Exhibit A1 are affected by bone growth and thus cannot be for proper assessment of changes caused by osteoporosis." (the written answer, page 21, lines 2 to 4)

"In Exhibit A1, the ash density of the entire femur of rats, which includes the cortical bone, was measured. Thus, it cannot be said that the effects of drugs on human osteoporosis, which are remarkably characterized by loss of trabecular bone, are disclosed." (the written statement on February 10, 2015, page 4, lines 4 to 6)

(h-3) Not experimented with multiple doses (the written answer, page 21, line 7)

(h-4) No significant effect of estrogen could be obtained in the model.

"It is stated that there was no significant effect of estradiol benzoate esters, which are estrogens that have been confirmed effective in humans and used for the actual treatment ERT. From this fact, a person skilled in the art has to recognize that the animal model of Exhibit A1 is not an effective model." (the written answer, page 21, line 23 to the last line)

(h-5) There are statistical defects.

"Exhibit A1 analyzed the experimental data by an erroneous statistical analysis method and incorrectly recognized statistically insignificant effects as a "statistically significant" effect. --- Exhibit A1 has obvious statistical defects." (the written answer, page 23, lines 4 to 8)

These matters (h-1) to (h-5) will be examined below.

Regarding (h-1)

The experiments stated in Exhibit B5, which are used by the demandee as the basis of the above claims, are carried out under conditions different from those stated in Exhibit A1, the conditions including places where animals were obtained, breeding conditions, the time period from ovariectomy to the date of evaluation, evaluation method, and so on. Even though Exhibit B5 did not show a decrease in bone density, therefore, it is not possible to deny the results stated in Exhibit A1 and to regard Exhibit A1 as being inappropriate as a reference.

Furthermore, the abstract of Exhibit B2 (page 69, left column, lines 11 to 15) states as follows: "The disadvantages of rats in the study of bones; that is, the development of modeling and growth of bone in the longitudinal direction, can be minimized by the use of slowly growing elderly rats and/or the use of the lamellar bone of the vertebral body or the secondary cancellous bone of long bone as a sample site." In the same exhibit, page 71, left column, lines 7 to 9, there is another statement that "In either case, the growth of longitudinal bone as a complex variable can be minimized by the use of elderly rats (9 to 12-month-old)." The use of 9 to 12-month-old elderly rats was known to be effective in minimizing the effects on bone growth in rats. Even if it is affected by pregnancy or lactation, it cannot be said that the 9-month old retired breeding rats used in Exhibit A1 are particularly inappropriate as animals used for osteoporosis studies.

In addition, both Exhibits B21 and B22 attached to the written statement dated October 27, 2014, which state retired breeding rats are inappropriate as osteoporosis models, are documents distributed after the priority date of the present application. On the priority date of this application, it could not be recognized that there was a common technical sense that retired breeding rats from which ovaries are removed are inappropriate as an osteoporosis model.

Regarding (h-2)

As stated in (c) and (d), a person skilled in the art who touched on Exhibit A1 could recognize that "ash density" and "bone density" are related to osteoporosis.

Then, according to the written answer, page 20, table 7, ovariectomized rats of Exhibit A1 showed an increase in calculated volume from baseline as much as normal rats but showed a negligible increase in ash weight. It can be therefore said that, relatively, a decrease in bone mass (decrease in density) without a decrease in bone volume occurs.

On the other hand, according to the statement in the Description of the Patent, paragraph [0002], it can be recognized that the term "osteoporosis" means that "a major debilitating disease whose prominent feature is the loss of bone mass (decreased density and enlargement of bone spaces) without a reduction in bone volume, producing porosity and fragility."

Thus, the ovariectomized rats of Exhibit A1 fit the above-stated features of "osteoporosis." It cannot be therefore said that the ash density measured in Exhibit A1 is not related to the bone density for the evaluation of osteoporosis.

Furthermore, Exhibit B3 is literature obtained by analyzing bone mineral content (BMC) by using a double photon absorption method (DPA) for ovariectomized rats (OX rats) and sham-ovariectomized rats (shOX rats). In Exhibit B3, page 103, right column, lines 13 to 19, there is a statement that "the minerals determined by BMC and ash as measured by DPA were compared in linear regression and corresponding t-test [25]. The calcium content is on average 42% of the ash weight. BMC measured by DPA correlates well with ash (Fig. 2, $r = 0.97$, $p < 0.001$). "

Further, in Exhibit B3, page 104, left column, lines 4 to 6, there is a statement that "BMC of the whole bone (Table 3) was 4.9 to 11.1% lower in OX rats than in shOX rats. In 35 to 100 days there was a significant difference." On the same page, right column, lines 1 to 3, there is a statement "the BMC of the distal femur (Table 4) was 12.5 to 17.5% lower in the OX rats than the shOX rats, and there was always a significant difference." Furthermore, on the same column, lines 13 to 15, there is a statement that "the femoral diaphysis BMC (Table 5) was more than 4.5% and less than 6.8% in OX rats and hOX rats. These differences were not significant."

According to these statements, although the measured values by DPA correlate with the measured values with ash and a difference in BMCs of the whole bones is smaller than that of the BMC of only the distal femur, it can be said that the influence by OX can be detected.

Thus, also with respect to the experimental results of Exhibit A1 showing the data of the entire bone due to ash density, the influence by OX can be detected, even though sensitivity is not as high as the test method used by the demandee. Likewise, the influence of the medicine is presumed to be detectable.

Therefore, it cannot be said that "ash density measured in Exhibit A1 is unrelated to bone density for evaluation of osteoporosis."

Regarding (h-3)

It is obvious to a person skilled in the art that if the effect is confirmed even if only a single dose is used, such an effect is sufficient for further research and development.

Regarding (h-4)

A person skilled in the art who touched on Described matter (L) Fig. 3 of Exhibit A1 could recognize that the estrogen-administered group tends to suppress a decrease in ash density even though there is no significant difference, as compared to the ovariectomy control group.

Regarding (h-5)

A person skilled in the art who touched on Described matter (L) Fig. 3 of Exhibit A1 could recognize that the raloxifene-administered group tends to suppress a decrease in ash density even though it is statistically defective, as compared to the ovariectomy control group.

Thus, a person skilled in the art who touched on Exhibit A1 could identify the demandee's allegation that the technical matter "a decrease in bone density due to rat ovariectomy was delayed by raloxifene, though not significantly."

(i) In addition, the demandee alleges that, for the reasons (i-1) to (i-3) below, there is an erroneous allegation in which Exhibit A1 states that refloxifine serves for maintaining bone density "without undesirable effects associated with estrogen therapy."

(i-1) The interpretation that tamoxifen of Exhibit A1 has no undesirable effects associated with estrogen therapy is contrary to technical common sense at the time of the priority date.
(i-2) Only the wet uterus weight is measured in Exhibit A1.
(i-3) The risk of uterine cancer is incorrectly stated in Exhibit A1.

These matters (i-1) to (i-3) will be examined below.

Regarding (i-1) and (i-3)

Exhibit A1 recognizes that tamoxifen has no estrogenic effect on the uterus. Such a recognition is certainly different from technical common sense at the time of the priority date. However, even if there is a misunderstanding about tamoxifen, the test results on raloxifene and the items derived therefrom are not denied.

Regarding (i-2)

Given the action of estrogens on the uterus, the uterine wet weight is an extremely general evaluation item (actually, the uterine wet weight is also evaluated in any of Exhibits A6 to A8). It cannot be said that there is an error in evaluating raloxifene such that raloxifene, which did not show weight gain effect as much as estrogen with respect to the uterine wet weight, has a small estrogenic effect on the uterus.

Furthermore, Fig. 2 of Exhibit A8 states that administration of 1 to 1000 μg of raloxifene (LY139481) to young rats results in smaller uterine weight than the administration of 0.1 μg of estradiol. It can be understood that the estrogenic effect of raloxifene on the uterus was known to be small before the priority date of this application.

Therefore, it cannot be said that "there is an erroneous allegation in which Exhibit A1 substantially states that refloxifine serves for maintaining bone density 'without undesirable effects associated with estrogen therapy.'"

(j) In addition, the demandee alleges the following matters.

(j-1) Difficulty in predicting the effects of Corrected Invention due to conflicting reports

"Exhibit B16 contradicts the conclusion stated in Exhibit A1." (the written answer, page 31, lines 4 to 5)
(j-2) Difficulty and bioavailability against the predictability of the effect of the Corrected Invention

"As a general view based on the publication on raloxifene at the time of the priority date of this application, raloxifene was recognized as one having low biological activity." (the written answer, page 32, lines 9 to 10)

These matters (j-1) and (j-2) will be examined below.

Regarding (j-1)

Exhibit B 16 is not literature aimed at the replication test of Exhibit A1; the experimental system and evaluation method of the former are different from the latter. The reliability of Exhibit A1 does not change even if the results are inconsistent with Exhibit B16. A person skilled in the art who touched on Exhibit A1 could predict without difficulty the effect that raloxifene is effective for osteoporosis.

Regarding (j-2)

A person skilled in the art could be clearly recognized to take, even if the bioavailability is low, any of various measures, such as adjusting the dose, derivatizing, and devising DDS, so long as the effect can be expected. Thus, it is not common to abandon the application to humans immediately as bioavailability is low.

Therefore, the allegations (h) to (j) of the demandee cannot be adopted.

As state above, Corrected Invention 1 could be easily provided by a person ordinarily skilled in the art according to the invention stated in Exhibit A1 and technical common sense at the time of the priority date. Thus, Corrected Invention 1 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act.

(2) Regarding Corrected Invention 2

Compare Corrected Invention 2 with Cited Invention.
As stated in (1) above, "keoxifene" of Cited Invention refers to "raloxifene hydrochloride" and thus corresponds to "raloxifene hydrochloride" of Corrected Invention 2.

Then, Corrected Invention 2 and Cited Invention are identical in terms of "a pharmaceutical formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the active ingredient of the pharmaceutical formulation is raloxifene hydrochloride," but at least literally different from each other in terms of the following feature:

- Corrected Invention 2 is "for treating or preventing human osteoporosis," while Cited Invention is characterized in that "9-month-old retired, ovariectomized female breeder rats were orally treated with raloxifene (100 μg) daily for 4 months for the purpose of confirming the effects of raloxifene on the bone density of elderly ovariectomized rats, and as a result a decrease in ash density due to ovariectomy was delayed significantly." (hereinafter, referred to as "Different feature 1").

- Corrected Invention 2 states that "causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the

uterus in rats, as compared with tamoxifen" but Cited Invention does not include such a statement (hereinafter, referred to as "Different feature 2").

Therefore, the above different features will be examined.

*Regarding Different feature 1

Different feature 1 is the same as Different feature 1 in the above (1). Thus, according to Cited Invention in a manner similar to the examination in the above (1), a person skilled in the art could easily conceive of applying to the treatment or prevention of human osteoporosis "a pharmaceutical formulation comprising raloxifene or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the active ingredient of the pharmaceutical formulation is raloxifene hydrochloride."

*Regarding Different feature 2

Regarding the statement "causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, as compared with tamoxifen" in Corrected Invention 2, even considering the description of the Detailed Description of the Invention, there is no mention that the dosage and administration, additives, etc. were examined in order to satisfy the condition "causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, as compared with tamoxifen."

Then, the above statement "causing less increase in height of the epithelium of the uterus and lower eosinophil infiltration into the stromal layer of the uterus in rats, compared with tamoxifen" can be recognized as one that merely states the inherent properties of "a pharmaceutical formulation comprising raloxifene or a pharmaceutical acceptable salt thereof as an active ingredient." It can be also recognized that such inherent properties of the pharmaceutical formulation can be those naturally imparted to a pharmaceutical formulation comprising raloxifene of Cited Invention as an active ingredient.

In this respect, therefore, it cannot be said that Corrected Invention 2 is an invention different from Cited Invention.

Thus, Corrected Invention 2 could be easily provided by a person ordinarily skilled in the art according to the invention stated in Exhibit A1 and technical common sense at the time of the priority day. Therefore, Corrected Invention 2 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act.

(3) Regarding Corrected Invention 3

Corrected Invention 3 is configured by addition to Corrected Invention 2 of an additional configuration of "the formulation is prepared for administration of raloxifene hydrochloride at 50 to 200 mg/day."

Comparing Corrected Invention 3 with Cited invention, in addition to Different features 1 and 2 in (2), Corrected Invention 3 is further different from Cited Invention in that "the formulation is prepared for administration of raloxifene hydrochloride at 50 to 200 mg/day."

Considering this matter, according to Described matter (H) Table 1 of Exhibit A1, the body weights of rats are 259 ± 20 g (base line) to 351 ± 42 g (ovariectomized).

Thus, an intermediate value of 300 g is set to a tentative body weight of the rat. Then, the dosage of raloxifene in Described matter (E) can be said to be 100 μg/300 g dose. Assuming that the body weight of a human is 60 kg, it corresponds to a dosage of approximately 20 mg. As alleged by the demandee in (j-2), the possibility that the bioavailability differs depending on the animal species is naturally considered. A person skilled in the art could easily provide a dosage suitable for humans with reference to the dosage in the rats and to make it into a unit dosage form containing an appropriate dosage.

Furthermore, in the Description of the Patent, paragraphs [0084] to [0092] state the protocols for human clinical trials, but do not state the results of the trials. Preparing 50 to 200 mg/day of raloxifene hydrochloride for administration cannot be recognized to exert any remarkable effect that exceeds the expectation of a person skilled in the art.

Thus, Corrected Invention 3 could be easily provided by a person ordinarily skilled in the art according to the invention stated in Exhibit A1 and technical common sense at the time of the priority day. Therefore, Corrected Invention 3 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act.

Furthermore, the demandee alleges that Exhibit A4 includes a statement in which raloxifene showed no effect. However, Exhibit A4 states the following matters: administration of 100-mg raloxifene hydrochloride to humans showed no antitumor activity but showed toxicity equivalent to tamoxifen (page 345, right column, line 6 to the last line). Exhibit A4 does not state the presence or absence of an effect of raloxifene hydrochloride on osteoporosis. Also, there was toxicity equivalent to tamoxifen which was actually used. Thus, the toxicity was negligibly minimal, so that hydrochloride could be applied to humans.

Therefore, the allegation of the demandee described above cannot be accepted.

(4) Regarding Corrected Invention 4

Corrected Invention 4 is configured by addition to Corrected Invention 1 of an additional configuration of "the formulation is in unit dosage form containing 50 to 200 mg of the active ingredient."

Comparing Corrected Invention 4 with Cited invention, in addition to Different features 1 and 2 in (1), Corrected Invention 4 is further different from Cited Invention in that "the formulation is in unit dosage form containing 50 to 200 mg of the active ingredient."

However, in a manner similar to the examination in the above (3), a person skilled in the art could easily provide a dosage suitable for humans with reference to the dosage in rats of Exhibit A1 and to make it into a unit dosage form containing an appropriate dosage.

In the Description of the Patent, paragraphs [0084] to [0092] state the protocols for human clinical trials, but do not state the results of the trials. Making it into a unit dosage form containing 50 to 200 mg of the active ingredient cannot be recognized to exert any remarkable effect that exceeds the expectation of a person skilled in the art.

(5) Regarding Corrected Invention 5

As examined in (1), "keoxifene" of Cited Invention is "raloxifene hydrochloride" and thus corresponds to "raloxifene hydrochloride" of Corrected Invention 5.

Then, there are no differences between Corrected Invention 5 and Cited Invention, except the matters examined in (4). As already discussed, it does not involve a so-called inventive step due to the above difference.

Therefore, Corrected Invention 5 could be easily provided by a person ordinarily skilled in the art according to the invention stated in Exhibit A1 and technical common sense at the time of the priority date. Thus, Corrected Invention 5 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act.

(6) Regarding Corrected Invention 6

Corrected Invention 6 is configured by addition to Corrected Invention 4 of an additional configuration of "the unit dosage form is prepared for oral administration."

Corrected Invention 6 and Cited Invention are different from each other in that "the unit dosage form is prepared for oral administration" in addition to the matters examined in (4).

However, since keoxifene of Cited Invention is used for "oral treatment," a person skilled in the art could easily conceive of preparing a unit dosage form for oral administration.

Thus, Corrected Invention 6 could be easily provided by a person ordinarily skilled in the art according to the invention stated in Exhibit A1 and technical common sense at the time of the priority date. Therefore, Corrected Invention 6 cannot obtain a patent in accordance with the provisions of Article 29(2) of the Patent Act.

No. 6 Conclusion

As stated above, the Patent for Corrected Inventions 1 to 6 was made in violation of the provisions of Article 29(2) of the Patent Act, and falls under Article 123(1)(ii) of the Patent Act, therefore should be invalidated .

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

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

April 15, 2015

Chief administrative judge: MURAKAMI, Kimitaka
Administrative judge: KAWAGUCHI, Yumiko
Administrative judge: NAITO, Shinichi