Patent Right	Date	October 11, 2018	Court	Intellectual Property High Court, First Division
	Case number	2017 (Gyo-Ke) 10165 2017 (Gyo-Ke) 10192		
- A case in which, with regard to a patent according to an invention titled "DOSAGES FOR TREATMENT WITH ANTI-ErbB2 ANTIBODIES," the Invention was easily conceivable since the constitution of the Invention was easily conceivable on the basis of Cited Document and the common general technical knowledge and it cannot be said that the constitution of the Invention causes significant unexpected effects.				

Case type: Rescission of Trial Decision of Invalidation

Result: Granted

References: Article 29, paragraph (2) of the Patent Act

Number of related rights, etc.: Patent No. 5818545, Invalidation Trial No. 2016-800071

Summary of the Judgment

1 This case is a suit for seeking a rescission against the trial decision, which concluded that there were no grounds for requesting a trial for patent invalidation against the defendant's patent according to the invention, titled "DOSAGES FOR TREATMENT WITH ANTI-ErbB2 ANTIBODIES." Invention 6 is generally a pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8 (the antibody), and the composition being intravenously administered in an initial dose of 8 mg/kg and subsequent doses of 6 mg/kg with an interval between each dose of 3 weeks (8/6/3 dosage regimen).

The trial decision concluded that there were no grounds for requesting a trial for patent invalidation, stating that the patent conforms to the enablement requirement and the inventive step requirement. In addition, the trial decision generally found Cited Invention 2-1 described in Cited Document 2 as a composition comprising the antibody to be administered in 4/2/1 dosage regimen.

2 The court decision rescinded the trial decision, stating that Invention 6 was easily conceivable on the basis of the cited invention and the common general technical knowledge with respect to the inventive step requirement as set forth below.

(1) Constitution

"A person ordinarily skilled in the art had had a common general technical knowledge as of the priority date that a larger dosage amount might possibly extend a dosing interval in common pharmaceutical products comprising a therapeutic agent for breast cancer, and a dose amount and a dosing interval were adjusted for observation

of efficacy and side effects in the development of pharmaceutical products, and the extension of the dosing interval might decrease the costs of hospital visit as well as pain and suffering in dosing for patients, and thus it was preferable from a viewpoint of cost efficiency and convenience."

"It can be said that Cited Document 2 suggests the possibility of administering the antibody in a dose amount up to 8 mg/kg or so once weekly.

Further, Cited Document 2 discloses a treatment method to combine weekly dose of the antibody with the dose of a chemotherapeutic agent every three week in a clinical test of the antibody.

Furthermore, Cited Document 2 discloses that the antibody shows dose-dependent pharmacokinetics, and the increase in a dose amount level may result in an extended half-life.

Consequently, a person ordinarily skilled in the art who has the above common general technical knowledge would easily try not only to administer the antibody in 4/2/1 dosage regimen as in Cited Invention 2-1, but also to adjust the dose amount and the dosing interval of the antibody while observing the efficacy and the side effects, and adjust the dose period of the antibody to 3 week in accordance with the dosing period of a chemotherapeutic agent to be combined from a viewpoint of cost efficiency and convenience, and increase the dosage amount of the antibody as necessary within a range up to 8 mg/kg or so. Further, a person ordinarily skilled in the art could have easily conceived of administering the antibody in 8/6/3 dosage regimen with an exercise of the ordinary inventive ability."

(2) The effects

"It was a common general technical knowledge for a person ordinarily skilled in the art as of the priority date that the extension of dosing interval was preferable for anticancer drug treatment from a viewpoint of cost efficiency and convenience. Consequently, as long as the effects comparable to Cited Invention 2-1 are not confirmed, it cannot be said from the only threefold extension of dosing interval that the effects of Invention 6 are unexpected and significant comparable to those of Cited Invention 2-1."

"The specification fails to describe extended time to disease progression or survival rate in a case of administering the antibody in 8/6/3 dosage regimen, and thus the therapeutic effects of Invention 6 are indefinite, and it cannot be instantly inferred that Invention 6 causes therapeutic effects comparable to those of Cited Invention 2-1.

Further, generally, the trough serum concentration is a minimum sustained efficacious drug concentration in the series of drug administrations ... Therefore, in a

case that the trough serum level to be sustained in the series of drug administrations, it is possible to assess that the efficacious drug concentration is all the more high and the therapeutic effects are also enhanced. However, comparing the trough serum concentrations of Cited Invention 2-1 and Invention 6, the trough serum concentration to be maintained in Cited Invention 2-1 is about 79 μg/ml, whereas the trough serum concentration to be maintained in Invention 6 is at most 17μg/ml. Consequently, it cannot be said that Invention 6 has therapeutic effects comparable to those of Cited Invention 2-1 even in terms of trough serum level.

In addition, the specification fails to describe the effects of suppressing side effects in a case of administering the antibody in 8/6/3 dosage regimen, and thus from the viewpoint of suppressing side effects, it cannot be said that Invention 6 causes therapeutic effects comparable to those of Cited Invention 2-1."

"Therefore, it cannot be recognized that Invention 6 has therapeutic effects comparable to those of Cited Invention 2-1."

Judgment rendered on October 11, 2018
2017 (Gyo-Ke) 10165 case of seeking rescission of JPO decision (Hereinafter referred to as "Ko case")
2017 (Gyo-Ke) 10192 case of seeking rescission of JPO decision (Hereinafter referred to as "Otsu case")
Date of conclusion of oral argument: September 18, 2018

Judgment

Plaintiff of the Ko case	Pfizer Holdings LLC
Plaintiff of the Otsu case	Celltrion Incorporated
Defendant of the Ko case and the Otsu case	Genentech, Incorporated

Main Text

1. The decision on Invalidation Trial No. 2016-800071 that JPO has made on July 5, 2017 shall be rescinded.
2. The Defendant of the Ko case and the Otsu case shall be bear the court costs.
3. For Defendant of the Ko case and the Otsu case , the additional period for filing a final appeal and a petition for acceptance of final appeal against this judgment shall be 30 days.

Facts and reasons

No. 1 Claim

The same as the item 1 of Main Text

No. 2 Summary of the case

1 History of the procedures etc. in Japan Patent Office

(1) Defendant of the Ko case and the Otsu case (hereinafter simply referred to as "Defendant") filed a patent application on July 8, 2011, titled "DOSAGES FOR TREATMENT WITH ANTI-ErbB2 ANTIBODIES" (a divisional application of Japanese Patent Application No. 2001-520142 (Priority date: August 27, 1999, June 23, 2000, United States)), and registered on October 9, 2015 (Japanese Patent No. 5818545, Number of claims: 9, Exhibit Ko 51, hereinafter this patent is referred to as "the Patent").

(2) Plaintiff of the Otsu case (hereinafter referred to as "Plaintiff Celltrion") requested a trial for patent invalidation with respect to the Patent on June 17, 2016, which was assigned to a collegial body as a case of Invalidation Trial No. 2016-800071 (Exhibit

Hei 302, 303). Thereafter, Plaintiff of the Ko case (hereinafter referred to as "Plaintiff Pfizer") participated in the trial (Exhibit Hei 313).

(3) Japan Patent Office made a decision on July 5, 2017 to the effect that "the trial of the case was groundless" as per attached written trial decision (copy) (hereinafter referred to as "the trial decision"), and on July 13 copies thereof were served to Plaintiff Celltrion and Plaintiff Pfizer. In addition, for Plaintiff Celltrion, 90 days are offered as a statute of limitations for filing a suit.

(4) Suits of seeking the rescission of the trial decision were filed by Plaintiff Pfizer on August 10, 2017 and Plaintiff Celltrion on October 30, 2017, respectively.

2 Recitation of the Claims

The recitation of Claims 1 to 9 of the scope of the claims of the Patent is set forth as below (Exhibit Ko 51). Hereinafter, the inventions according to the claims are referred to as "Invention 1," etc. according to the number of the claim, and are collectively referred to as "each of the Inventions." Further, the specification (Exhibit Ko 51) is referred to as "the specification" including the drawings.

[Claim 1] A package comprising: (i) a container containing a pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered at an initial dose of 8 mg/kg and a plurality of subsequent doses of 6 mg/kg at an interval between each dose of said antibody of 3 weeks; and (ii) a package insert attached to the container.

[Claim 2] The package of Claim 1, further comprising a second container comprising a pharmaceutically-acceptable buffer.

[Claim 3] The package of Claim 2, wherein the pharmaceutically-acceptable buffer is phosphate-buffered saline, Ringer's solution, or dextrose solution.

[Claim 4] The package of any one of Claims 1 to 3, wherein said package insert contains instructions to avoid the use of anthracycline-type chemotherapeutics in combination with the composition.

[Claim 5] The package of Claim 4, wherein anthracycline-type chemotherapeutic agent is doxorubicin or epirubicin.

[Claim 6] A pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered at an initial dose of 8 mg/kg and a plurality of subsequent doses of 6 mg/kg at an interval between each dose of said antibody of 3 weeks.

[Claim 7] The pharmaceutical composition of Claim 6, further comprising a

pharmaceutically-acceptable buffer.

[Claim 8] The pharmaceutical composition of Claim 7, wherein the pharmaceutically-acceptable buffer is phosphate-buffered saline, Ringer's solution, or dextrose solution.

[Claim 9] The pharmaceutical composition according to any one of Claims 6 to 8, which is co-administered with a chemotherapeutic agent.

3 Abstract of reasons of trial decision

(1) The reason for trial decision is as per the attached written trial decision (copy). In summary, [i] the Detailed Description of the Invention of the specification discloses definitely and sufficiently to the extent that allows a person ordinarily skilled in the art to implement the Invention, and thus conforms to the requirement as provided in Article 36, paragraph(4) of the Patent Act before the revision by Act No. 24 of 2002 (hereinafter referred to as "enablement requirement") [ii] i) Inventions 1 to 5 were not easily conceivable by a person ordinarily skilled in the art on the basis of the invention according to the product described in Cited Document 1 in the following item A (hereinafter referred to as "Cited Invention 1-2") and the invention described in Cited Documents 2 to 6 in the following B to F, and Inventions 6 to 9 were easily conceivable on the basis of the inventions according to a composition described in Cited Document 1 (hereinafter referred to as "Cited Invention 1-1") and the invention described in Cited Documents 2 to 6, ii) The Inventions 1 to 5 were easily conceivable by a person ordinarily skilled in the art on the basis of the invention according to the package described in Cited Document 2 (hereinafter referred to as "Cited Invention 2-2") and the invention described in Cited references 1, 3 to 6, and Inventions 6 to 9 were easily conceivable by the invention according to the composition described in Cited Document 2 (hereinafter referred to as "Cited Invention 2-1") and the invention described in Cited Documents 1, 3 to 6, and iii) the each of the Inventions was easily conceivable by the invention according to the composition described in Cited Document 3 (hereinafter referred to as "Cited Invention 3") and the inventions described in Cited Documents 1, 2, 5, and 6, and thus the Inventions should not be granted a patent under the provision of Article 29, paragraph(2) of the Patent Act.

A Cited Document 1: International Publication No. WO 1999-31140 (published in June 1999, Exhibit Ko 1)

B Cited Document 2: Package Insert of Pharmaceutical product Herceptin (registered trademark) approved in the United States (published in 1998, Exhibit Ko 2)

C Cited Document 3: Toru WATANABE et al., Program and Abstracts of "The sixth annual meeting of Japan Breast Cancer Society" (held in 1998), page 59, A-121 (Exhibit Ko 3)

D Cited Document 4: A website titled "Phase II Study of Paclitaxel, Carboplatin, and trastuzumab (Herceptin) as First-Line Chemotherapy in Women With Overexpressed HER-2, Metastatic Breast Cancer" (published by National Cancer Institute (NCI). http://web.archive.org/web/20111023025823/http://cancer.gov/clinicaltrials/search/view?cdrid=66689&version=healthprofessional), electronic technical information (searched in 2013. Exhibit Ko 4)

E Cited Document 5: Kanji TAKADA, Shozo, ASADA, "Essential of Pharmacokinetics" (Hirokawa-Shoten Ltd., second printing on February 25, 1979), pages 70 to 85 (Exhibit Ko 5)

F Cited Document 6: "New Current 9(24)", November 1, 1998, pages 36 to 37, (Exhibit Ko 6)

(2) Comparison between each of the Inventions and the invention described in Cited Document 1

A The trial decision found Cited Invention 1-2 as well as the Common Features and the Differences between Invention 1 and Cited Invention 1-2 as set forth below: Additionally, the symbol "/" indicates a part of carriage return in the original text.

(A) Cited Invention 1-2

A product comprising a container, a composition comprising the container, and a package insert including an instruction to avoid the use of anthracycline-type chemotherapeutic agent in combination with the composition, wherein the composition is a composition comprising a humanized version of the murine 4D5 antibody (Herceptin (registered trademark)) for the treatment of breast cancer, characterized by the overexpression of ErbB2 receptor in combination with a chemotherapeutic agent other than anthracycline derivatives, and wherein the antibody is intravenously administered at 4 mg/kg at Day 0, and one week later, followed by subsequent doses of 2 mg/kg weekly.

(B) Common Features and Differences between Invention 1 and Cited Invention 1-2

a Common Features

A package comprising: a container containing a pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered at an initial dose and a plurality of the subsequent doses with an interval between each dose of said antibody; and a package insert attached to the container

b Difference 1

Further, Invention 1 implements "the intravenous administration" of "anti-ErbB2 antibody huMab4D5-8" "at an initial dose of 8 mg/kg and a plurality of the subsequent doses of 6 mg/kg at an interval between each dose of said antibody of 3 weeks," whereas Cited Invention 1-2 implements "the intravenous administration" of "anti-ErbB2 antibody huMab4D5-8" "at an initial dose of 4 mg/kg and a plurality of subsequent doses of 2 mg/kg at an interval between each dose of said antibody of 1 week"

B The trial decision found Cited Invention 1-1 as well as the Common Features and the Differences between Invention 6 and Cited Invention 1-1 as set forth below:

(A) Cited Invention 1-1

A composition comprising a humanized version of the murine 4D5 antibody (Herceptin (registered trademark)) for the treatment of breast cancer characterized by the overexpression of ErbB2 receptor in combination with a chemotherapeutic agent other than anthracycline derivatives, and wherein the antibody is intravenously administered at 4 mg/kg on Day 0, and one week later, followed by subsequent doses of 2 mg/kg weekly.

(B) Common Features and Differences between Invention 6 and Cited Invention 1-1

a Common Features

A pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibodyhuMab4D5-8, and the composition being intravenously administered

b Differences

The same as Difference 1.

(3) Comparison between each of the Inventions and the invention described in Cited Document 2

A The trial decision found Cited Invention 2-2 as well as the Common Features and the Differences between Invention 1 and Cited Invention 2-2 as set forth below:

(A) Cited Invention 2-2

A package comprising: a container filled with a composition for the treatment of metastatic breast cancer characterized by the overexpression of HER2, the composition comprising Herceptin (registered trademark), and the composition being intravenously administered in a loading dose of 4 mg/kg Herceptin and a subsequent maintenance dose of 2 mg/kg per week; and Efficacy and a notice of Herceptin

(B) Common Features and Differences between Invention 1 and Cited Invention 2-2

a Common Features

A package comprising: a container containing a pharmaceutical composition for

the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered at an initial dose and a plurality of the subsequent doses with an interval between each dose of said antibody; and a package insert attached to the container

b Difference 2

Further, Invention 1 implements "the intravenous administration" of "anti-ErbB2 antibody huMab4D5-8" "at an initial dose of 8 mg/kg and a plurality of the subsequent doses of 6 mg/kg at an interval between each dose of said antibody of 3 weeks," whereas Cited Invention 2-2 implements "the intravenous administration" of "anti-ErbB2 antibody huMab4D5-8" "at an initial dose of 4 mg/kg and a plurality of subsequent doses of 2 mg/kg at an interval between each dose of said antibody of 1 week"

B The trial decision found Cited Invention 2-1 as well as the Common Features and the Differences between Invention 6 and Cited Invention 2-1 as set forth below:

(A) Cited Invention 2-1

A composition for the treatment of metastatic breast cancer characterized by the overexpression of HER2, the composition comprising Herceptin (registered trademark), and the composition being intravenously administered at a loading dose of 4 mg/kg Herceptin and a subsequent maintenance dose of 2 mg/kg per week

(B) Common Features and Differences between Invention 6 and Cited Invention 2-1

a Common Features

A pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered

b Differences

The same as Difference 2.

(4) Comparison between each of the Inventions and the invention described in Cited Document 3

The trial decision found Cited Invention 3 as well as the Common Features and the Differences between Inventions 1 and 6 and Cited Invention 3 as set forth below:

A Cited Invention 3

A composition for infusion comprising MKC-454 for the treatment of metastatic breast cancer characterized by the overexpression of HER2, wherein 8 mg/kg of MKC-454 is initially administered by infusion, which is followed by repetitive weekly equal doses from 3 weeks after the initial dose, with a total of ten

doses.

B Common Features and Differences between Invention 1 and Cited Invention 3

(A) Common Features

A pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered at an initial dose of 8 mg/kg with an interval between each dose of said antibody

(B) Difference 3

Invention 1 implements "each dose with an interval of 3 weeks" with "a plurality of the subsequent doses" of "6 mg/kg," whereas Cited Invention 3 implements "a plurality of the subsequent doses" of "8 mg/kg" with an interval between the initial dose and the second dose of 3 weeks and with an interval between doses after the second dose of 1 week

(C) Difference 4

Invention 1 relates to "a package" comprising "a pharmaceutical composition" as well as "a container including a pharmaceutical composition" and "a package insert accompanied with the container," whereas Cited Invention 3 does not particularly specify such package form comprising a container and a package insert

C Common Features and Differences between Invention 6 and Cited Invention 3

(A) Common Features

A pharmaceutical composition for the treatment of breast cancer characterized by the overexpression of HER2, the composition comprising anti-ErbB2 antibody huMab4D5-8, and the composition being intravenously administered at an initial dose of 8 mg/kg with an interval between each dose of said antibody

(B) Differences

The same as Difference 3.

4 Abbreviation of the descriptions of antibodies and dose/dose regimen

Anti-ErbB2 antibody huMab4D5-8 is sometimes referred to as "the antibody."

Further, "a dosage regimen of the intravenous administration of the antibody at an initial dose of 8 mg/kg and a plurality of the subsequent doses of 6 mg/kg at an interval between each dose of said antibody of 3 weeks" is referred to as "8/6/3 dosage regimen," and "a dosage regimen of the intravenous administration of the antibody at an initial dose of 4 mg/kg and a plurality of the subsequent doses of 2 mg/kg at an interval between each dose of said antibody of 1 week" is sometimes referred to as "4/2/1 dosage regimen."

5 Grounds for rescission

(1) Error in the determination of the enabling requirement (Grounds 1 for rescission)
(2) Error in the determination of the inventive step on the basis of Cited Inventions 1-1 and 1-2 (Grounds 2 for rescission)
(3) Error in the determination of the inventive step on the basis of Cited Inventions 2-1 and 2-2 (Grounds 3 for rescission)
(4) Error in the determination of the inventive step on the basis of Cited Invention 3 (Grounds 4 for rescission)

(omitted)

No. 4 Judgment of this court
1 As for Invention 6
(1) The description of the specification

The scope of the Claims of Invention 6 is set forth as in the aforesaid [Claim 6] of No. 2, the item 2. The specification (Exhibit Ko 51) generally has the following descriptions. Note that the specification describes Table 2 and Figure 3 as per the attached list of Drawings and Tables of the specification:

A Field of the Invention

[0001] The present invention concerns the treatment of disease characterized by the overexpression of ErbB2. More specifically, ... the treatment is with an anti-ErbB2 antibody administered by front loading the dose of antibody during treatment by intravenous and/or subcutaneous administration. ...

B Background Art

[0002] ... the human ErbB2 gene (erbB2, or also known as her2, or c-erbB-2) is overexpressed in about 25% to 30% of cases of human breast cancer ...

[0011] A recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as ... Herceptin, or Herceptin anti-ErbB2 antibody) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy. ... The initial injection of 4 mg/kg of the recommended Herceptin is administered over 90 minutes. A weekly recommended maintenance dose is 2 mg/kg, and should the initial injection be well accepted, it may be administered over 30 minutes.

C Summary of the Invention

[0013] The present invention relates to the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of

anti-ErbB2 antibodies followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments. ... The target serum concentration is thereafter maintained by the administration of maintenance doses of equal or smaller amounts for the remainder of the treatment regimen or until suppression of disease symptoms is achieved. ...

[0014] ... The front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment. ...

[0018] The present application also provides a method of therapy involving infrequent dosing of an anti-ErbB2 antibody. ...

[0020] ... Preferably the antibody is ... huMAb4D5-8 (Herceptin anti-ErbB2 antibody). ...

[0044] ... The term "peak serum concentration" refers to the maximal serum drug concentration shortly after delivery of the drug into the animal or human patient, after the drug has been distributed throughout the blood system, but before significant tissue distribution, metabolism, or excretion of drug by the body has occurred. The term "trough serum concentration" refers to the serum drug concentration at a time after delivery of a previous dose and immediately prior to delivery of the next subsequent dose of drug in a series of doses. Generally, the trough serum concentration is a minimum sustained efficacious drug concentration in the series of drug administrations. ...

D Example 2: Pharmacokinetic and pharmacodynamics properties of anti-ErbB2 antibody (Herceptin)

[0102] ... An initial dose of 4 mg/kg Herceptin anti-ErbB2 antibody is administered by an intravenous administration, and followed by a weekly intravenous administration of 2 mg/kg Herceptin anti-ErbB2 antibody for several weeks. ...

[0103] The Herceptin anti-ErbB2 antibody trough serum concentrations from Week 2 through Week 36 are plotted in Figure 3 (dark circles). ... Trough serum concentrations tended to increase through Week 12 and tended to plateau after that time.

[0106] The data in Table 2 suggest that there was an increase in trough serum concentration over time. ...

[0107] Patient response status was evaluated relative to serum concentration of Herceptin anti-ErbB2 antibody. ... The increase in serum concentration between Weeks 2 and 8 appeared to be greater in responders than in nonresponses, suggesting that there is a relationship between response status and Herceptin anti-ErbB2

antibody serum concentration. ...

E Example 5: Regimens for Intravenous and Subcutaneous Delivery of Anti-ErbB2 Antibody

[0114] In another method, an initial (front loading) dose of 8 mg/kg Herceptin anti-ErbB 2 antibody is delivered by intravenous injection. This is followed by intravenous bolus injections ... of 6 mg/kg at 3-week intervals to maintain a trough serum concentration of approximately 10 to 20 μg/ml, averaged for an entire treatment group.

F Example 6: Herceptin Administered Intravenously Every Three Weeks in Combination with Paclitaxel

[0116] Currently, the recommended dose of Herceptin is 2 mg/kg once weekly. Patients will be administered Herceptin every three weeks instead of weekly, along with paclitaxel (175 mg/m^2 every three weeks). Simulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 mcg/ml, in the range (10 to 20 mcg/ml) of the targeted trough serum concentrations from previous Herceptin IV clinical trials. ...

(2) Features of Invention 6

According to the aforesaid item (1), the Features of the Invention 6 are as set forth below.

A The antibody is a clinically active monoclonal antibody in breast cancer patients with the overexpression of human ErbB2 gene (Her2). Invention 6 is a pharmaceutical composition for the use in the therapy using the antibody. ([0001], [0002], [0011])

The conventional technique of therapy using the antibody was to administer 4/2/1 dosage regimen. ([0011])

B Invention 6 is based on the discovery that early achievement of the minimum drug level is more effective compared to the conventional therapy in a case of continuous dose of the antibody, and the antibody is used for a therapy to administer the antibody in 8/6/3 dosage regimen. ([0013], [0044])

C Invention 6 increases the therapeutic effects of the use of the antibody and allows for less frequent doses of the antibody. ([0014], [0018])

2 Grounds 3 for rescission (Error in the determination of the inventive step on the basis of Cited Inventions 2-1 and 2-2)

In view of the nature of the case, the grounds 3 for rescission are firstly considered in the following.

(1) Cited Invention 2-1

Cited Document 2 (Exhibit Ko 2) is a package insert of the pharmaceutical product Herceptin (trastuzumab) approved in the United States, whereas there is no dispute between the parties with regard to the fact that Cited Document 2 describes Cited Invention 2-1 as in the aforesaid No. 2, item 3(3)B(A). Further, Cited Document 2 generally discloses the following point with respect to Cited Invention 2-1:

A Pharmacokinetics (page 1, left column)

The pharmacokinetics of trastuzumab was studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg Herceptin once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 mg and 500 mg dose levels, respectively. ...

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range = 1 to 32 days) was observed. Between Weeks 16 and 32, trastuzumab serum concentrations reached a steady state with a mean trough and peak concentrations of approximately 79 μg/ml and 123 μg/ml, respectively. ...

B Clinical studies (page 1, left column)

... A multicenter, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Patients were randomized to receive chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). ...

Compared with patients randomized to chemotherapy alone, the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate. ...

(2) Comparison between Invention 6 and Cited Invention 2-1

There is no dispute between parties with regard to the fact that the Differences between Invention 6 and Cited Invention 2-1 is as in the aforesaid No. 2, 3(3)B(B)b.

(3) Common general technical knowledge

A Dose amount and interval of pharmaceutical products

(A) "Guideline for consideration of dose-response relationship - Necessary for approval of new pharmaceutical products," notified by a director of the Examination Division of Pharmaceutical Affairs Bureau (July 25, 1994) (Exhibit Hei 323-1)

Exhibit Hei 323-1 is a document in which a director of the Examination Division of Pharmaceutical Affairs Bureau requested directors of sanitation departments with primary responsibility in each prefecture to inform businesses concerned under the jurisdiction of "new guideline for consideration of dose-response relationship - Necessary for approval of new pharmaceutical products."

The guideline collects necessary dose-response information over the whole period of the development of pharmaceutical products, and shows a guideline of methodology to be considered for providing beneficial information on the use of the pharmaceutical products in the subsequent clinical tests and the market.

Further, the guideline discloses that "The selection of dose amount for individual patients is often associated with dosage frequency. In general, in a case that the dosing interval is longer than a half-life of drug, attention should be paid to pharmacokinetically explain the selected dosing interval. For example, a comparison should be made between a longer dosing interval and a frequent dose with short intervals for the same dose amount. In the case, if possible, whether the expected effects are sustained until the next dose and side effects at a peak of blood level are observed." (page 3).

(B) M. A. Richards et al., "Doxorubicin in Advanced Breast Cancer: Influence of Schedule on Response, Survival and Quality of Life", The European Journal of Cancer 28A 6/7, pages 1023 to 1028 (May 1992) (Exhibit Hei 328)

Exhibit Hei 328 discloses that "Doxorubicin is usually administered every three week, but a weekly dose is also effective, possibly decreasing the occurrence of cardiac toxicity." "In this study, metastatic breast cancer patients who had not undergone cytotoxic chemotherapy previously in a progressive disease were randomized for two comparable dose regimens; i.e., weekly dose of 25 mg/m^2 doxorubicin or every 3 week dose of 75 mg/m^2." and furthermore, it discloses that "As a result, two doxorubicin dose regimens used for this study had the same dose intensity and effects." (page 1023, page 1027).

(C) J. E. Ferguson et al., "High Dose, dose-intensive chemotherapy with doxorubicin and cyclophosphamide for the treatment of advanced breast cancer" (1993) (Exhibit Hei 329)

Exhibit Hei 329 discloses that "The importance of drug scheduling and dose

intensity on efficacy and toxicity of treatment have been increasingly appreciated. When the total dose of two regimens are equivalent, the dose intensity may be of critical importance as exemplified by the lower efficacy of 35 mg/m^2 doxorubicin (3 weeks x 16) when compared to 70 mg/m^2 doxorubicin (3 weeks x 8)... . In a randomized study comparing the effect of scheduling on treatment outcome, there was no difference between the equidose intensive regimens of doxorubicin 25 mg/m^2 (weekly x 12) versus 75 mg/m^2 (3 weekly x 4)... ." (page 825, left column).

(D) According to each description of Exhibit Hei 323-1, 328, and 329, it was a matter of common general technical knowledge for a person ordinarily skilled in the art as of the priority date that a larger dosage amount might possibly extend dosing interval in common pharmaceutical products comprising a therapeutic agent for breast cancer, and dose amount and dosing interval were adjusted for observation of efficacy and side effects in the development of pharmaceutical composition.

B Less frequent dosing

(A) Japanese Unexamined Patent Application Publication No. 1995-187994 (Exhibit Ko 12)

Exhibit Ko 12 discloses that "Most proteinaceous drugs exhibit very short half-lives in the blood, e.g., a few minutes to a few hours, and as a result it becomes necessary to administer them at frequent intervals in order to achieve long-term maintenance of the drug concentration in the blood within therapeutic ranges. ... the use of injectable drug formulations of this type places a very heavy burden on the patient because it requires frequent hospital treatment or outpatient visits and causes pain at the time of administration. Given the foregoing circumstances, it is desirable to develop a controlled release drug formulation that is capable of maintaining the therapeutic efficacy of water-soluble drugs, such as proteins, over prolonged periods after a single administration." ([0002]).

(B) Mace L. Rothenberg et al., "Alternative Dosing Schedules for Irinotecan", Oncology, Vol. 12, No. 8, Attachment 6, page 68 (August 1998) (Exhibit Ko 17)

Exhibit Ko 17 discloses that "many drugs, including irinotecan, have a clear dose-response relationship in vitro. This suggests that irinotecan should be given at the highest single dose possible in order to achieve maximal antitumor effect. ... In addition to exploiting the dose-response relationship, this approach has the added advantage of greater patient convenience, as it entails less frequent dosing than is required on a weekly schedule." (page 69, left column to middle column).

(C) According to the description of Exhibit Ko 12 and Exhibit Ko 17, it was a matter of common general technical knowledge for a person ordinarily skilled in the art as of

the priority date that the extension of dosing interval was preferable for anticancer drug treatment from a viewpoint of cost efficiency and convenience because it decreases the costs of hospital visits and pain and suffering in dosing for patients.

(4) Inventive step of Invention 6

A As for the constitution

(A) A consideration is given as to whether a person ordinarily skilled in the art could have easily conceived of the constitution of Invention 6 according to Difference 2; i.e., replacing the administration of the antibody in 4/2/1 dosage regimen according to Cited Invention 2-1 with the administration of the antibody in 8/6/3 dosage regimen according to Invention 6.

(B) As aforementioned, a person ordinarily skilled in the art had a common general technical knowledge as of the priority date that a larger dosage amount might possibly extend dose interval in common pharmaceutical products comprising a therapeutic agent for breast cancer, and dose amount and dose interval were adjusted for observation of efficacy and side effects in the development of pharmaceutical composition, and the extension of the dose interval might decrease the cost of hospital visit and pain and suffering in dosing for patients, and thus it is preferable from a viewpoint of cost efficiency and convenience.

Further, Cited Document 2 discloses that the intravenous infusion of the antibody for a short sustained period of 10 to 500 mg once weekly was implemented in observing pharmacokinetics of the antibody. Here, once weekly dosing of 10 to 500 mg corresponds to 0.167 to 8.33 mg/kg in a case of patients' body weight of 60 kg, and 0.143 to 7.14 mg/kg in a case of patients' body weight of 70 kg. Consequently, it can be said that Cited Document 2 suggests the possibility of administering the antibody in a dose amount up to 8 mg/kg or so once weekly.

Further, Cited Document 2 discloses a treatment method to combine weekly dose of the antibody with the dose of a chemotherapeutic agent every three week in a clinical test of the antibody.

Furthermore, Cited Document 2 discloses that the antibody shows dose-dependent pharmacokinetics, and the increase in a dose amount level may result in an extended half-life.

Consequently, a person ordinarily skilled in the art who has the above common general technical knowledge would easily try not only to administer the antibody in 4/2/1 dosage regimen as in Cited Invention 2-1, but also to adjust the dose amount and the dose interval of the antibody while observing the efficacy and the side effects, and adjust the dose period of the antibody to 3 week in accordance with the dosing period

of chemotherapeutic agent to be combined from a viewpoint of cost efficiency and convenience, and increase the dosage amount of the antibody as necessary within a range up to 8 mg/kg or so. Further, a person ordinarily skilled in the art could have easily conceived of administering the antibody in 8/6/3 dosage regimen with an exercise of the ordinary inventive ability.

(C) Defendant's allegation

Defendant argues that only the 4/2/1 dosage regimen was clinically used before the priority date, and the half-life of the antibody was supposed to be 1 week or so, and thus it cannot be said as the optimization of technique to adjust the dosing interval to 3 weeks, which is far beyond the half-life as like 8/6/3 dosage regimen.

However, Cited Document 2 suggests the possibility of administering in a dose amount up to 8 mg/kg or so once weekly, and further the increase in a dose amount level of the antibody may result in a prolonged half-life. Furthermore, Exhibit Hei 323-1 discloses a notice, which supposes that a dosing interval being longer than a half-life. Further, if a person ordinarily skilled in the art who has the aforementioned common general technical knowledge should exercise ordinary creativity, it was easily conceivable to replace the administration of the antibody in 4/2/1 dosage regimen with the administration of the antibody in 8/6/3 dosage regimen. In addition, the declaration of Doctor A (Exhibit Otsu 8) discloses that oncologists would not be motivated to administer the antibody in 8/6/3 dosage regimen, since the experiment of untested dosage regimen might expose patients' lives at risk; however, the lack of motivation in clinicians to clinically try new dosage and dose regimen of a drug does not negate motivation to try the development of new dosage and dose regimen of the drug.

(D) Therefore, a person ordinarily skilled in the art could easily conceive of the configuration of Invention 6 according to Difference 2 on the basis of Cited Document 2 and the common general technical knowledge.

B The effects caused

(A) In determining the inventive step of Invention 6 on the basis of Cited Invention 2-1, one should consider not only whether it is easy to conceive of the constitution of Invention 6 according to Difference 2, but also whether or not Invention 6 causes unexpected and significant effects. It is a Patentee; i.e., Defendant, who should argue and establish the fact supporting that Invention 6 causes unexpected and significant effects.

Further, in the case, the Defendant argues that Invention 6 to administer the antibody in 8/6/3 dosage regimen has therapeutic effects comparable to those of Cited

Invention 2-1 to administer in 4/2/1 dosage regimen, and the dosing interval becomes tripled, and thus Invention 6 causes significant effects.

(B) Dosing interval

a Invention 6 to administer the antibody in 8/6/3 dosage regimen has a tripled dosing interval compared to Cited Invention 2-1 to administer 4/2/1 dosage regimen, which reduces pain and suffering in dosing for patients, and thus is excellent from the viewpoint of cost efficiency and convenience.

As aforementioned, however, it was a matter of common general technical knowledge for a person ordinarily skilled in the art as of the priority date that the extension of dosing interval was preferable for anticancer drug treatment from a viewpoint of cost efficiency and convenience. Consequently, as long as effects comparable to those of Cited Invention 2-1 are not confirmed, the threefold extension of dosing interval cannot be a ground for the fact that the effects of the Invention 6 are unexpected and significant comparable to those of Cited Invention 2-1.

b In addition, in view of the fact that the target trough serum level of the previous clinical trials according to the antibody fell within a range of 10 to 20 μg/ml, the maintenance of this range of trough serum concentration would result in comparable therapeutic effects, and Invention 6 suggesting the trough serum concentration of 17 μg/ml may also be assessed as indicating that therapeutic effects might be achieved. Consequently, 8/6/3 dosage regimen triples dosing interval compared to Cited Invention 2-1, while maintaining comparable therapeutic effects.

Cited Document 2 discloses, however, that the antibody shows dose-dependent pharmacokinetics, and the increase in a dose amount level may result in an extended half-life, and the administration of the antibody in 4/2/1 dosage regimen could maintain the trough serum concentration of about 79 μg/ml. Further, it may be expected from this description that the administration of the antibody in 8/6/3 dosage regimen could maintain the trough serum concentration of 17 μg/ml or so.

Consequently, setting aside the enablement requirement and supporting requirement, when it comes to the inventive step, it cannot be recognized that the therapeutic effects of Invention 6 are unexpected and significant comparable to those of Cited Invention 2-1 on the basis of the fact of threefold extension of dosing interval of Invention 6 while maintaining therapeutic effects to the extent that were required in the previous clinical trials.

(C) Therapeutic effects

a Cited Document 2 mentions therapeutic effects in a case of the administration of the antibody in 4/2/1 dosage regimen that between Weeks 16 and 32, trastuzumab

serum concentrations reached a steady state with a mean trough and peak concentration of approximately 79 μg/ml and 123 μg/ml, respectively, and that compared with the case of chemotherapy alone, it resulted in a significantly longer median time to disease progression and a higher one-year survival rate.

b On the other hand, in a case where the antibody is administered in the 8/6/3 dosage regimen, the specification discloses "maintain a trough serum concentration of approximately 10 to 20 mcg/ml" ([0114]), and "suggests that the trough serum concentrations will be 17 mcg/ml, in the range (10 to 20 μg/ml) of the targeted trough serum concentrations from previous Herceptin IV clinical trials." ([0116]). Indeed, the specification fails to describe extended time to disease progression or survival rate in a case of administering the antibody in 8/6/3 dosage regimen.

c Incidentally, the specification fails to describe extended time to disease progression or survival rate in a case of administering the antibody in 8/6/3 dosage regimen, and thus the therapeutic effects of Invention 6 are indefinite, and it cannot be instantly inferred that Invention 6 causes therapeutic effects comparable to those of Cited Invention 2-1.

Further, generally, the trough serum concentration is a minimum sustained efficacious drug concentration in the series of drug administrations (the specification [0044]). Therefore, in a case that the trough serum level to be sustained in the series of drug administrations, it is possible to assess that the efficacious drug concentration is all the more high and the therapeutic effects are also enhanced. However, comparing the trough serum concentrations of Cited Invention 2-1 and Invention 6, the trough serum concentration to be maintained in Cited Invention 2-1 is about 79 μg/ml, whereas the trough serum concentration to be maintained in Invention 6 is at most 17 μg/ml. Consequently, it cannot be said that Invention 6 has therapeutic effects comparable to those of Cited Invention 2-1 even in terms of trough serum level.

In addition, the specification fails to describe the effects of suppressing side effects in a case of administering the antibody in 8/6/3 dosage regimen, and thus from the viewpoint of suppressing side effects, it cannot be said that Invention 6 causes therapeutic effects comparable to those of Cited Invention 2-1."

d Therefore, it cannot be recognized that Invention 6 has therapeutic effects comparable to those of Cited Invention 2-1.

(D) Defendant's allegation

a Defendant argues that a simulation of data disclosed in Table 2 and Figure 3 of the specification allows us to confirm therapeutic effects in a case of administering the antibody in 8/6/3 dosage regimen.

Specifically, all data disclosed in Table 2 and Figure 3 of the specification disclose a profile of trough serum concentration in a case of administering the antibody in 4/2/1 dosage regimen. Further, the declaration of Doctor B (Exhibit Ko 32) analyzes pharmacokinetics of the antibody by use of an analysis software "Berkeley Madonna™". The declaration mentions that pharmacokinetic parameters of the antibody may be obtained from data disclosed in Table 2 and Figure 3 of the specification, and if one should run a simulation with these parameters in 8/6/3 dosage regimens, "it would go far beyond a level at which it had been identified as effective, and would easily maintain a Herceptin plasma level similar to a level at which the treatment of patient made a success in a clinical test (A trough concentration is slightly lower than that achieved from 4/2/1 dosage regimen, but much higher than a minimum target of 10 μg/ml)."

Furthermore, in view of the fact that Cited Document 2 discloses that the antibody shows dose-dependent pharmacokinetics, and the increase in a dose amount level may result in an extended half-life, it is recognized that pharmacokinetics may differ between the case of administering the antibody in 4/2/1 dosage regimen and the case of administering the antibody in 8/6/3 dosage regimen. Consequently, if parameters obtained by analyzing data disclosed in Table 2 and Figure 3 of the specification are correct, these parameters are at most parameters in a case of administering the antibody in 4/2/1 dosage regimen, and it is not appropriate to simulate pharmacokinetics in a case of administering the antibody in 8/6/3 dosage regimen with these parameters (Expert opinion of associate professor C, pages 11 to 13 (Exhibit Ko 54)).

Therefore, the court cannot accept the description of the declaration of Dr. Grass at face value that the trough serum concentration in a case of administering the antibody in 8/6/3 dosage regimen is slightly lower than that achieved by 4/2/1 dosage regimen on the basis of data analysis disclosed in Table 2 and Figure 3 of the specification.

Further, it is recognized that the increased dose amount level of the antibody may result in a prolonged half-life; however, the specification fails to describe to what extent it prolongs half-life, which was not clearly found as of the priority date. It is indefinite as to how much the trough serum concentration exceeds 17 μg/ml in a case of administering the antibody in 8/6/3 dosage regimen.

Therefore, it cannot be confirmed on the basis of data disclosed in Table 2 and Figure 3 of the specification that the therapeutic effects in a case of administering the antibody in 8/6/3 dosage regimen are comparable to those of 4/2/1 dosage regimen.

b Defendant argues that therapeutic effects in a case of administering the antibody in 8/6/3 dosage regimen are objectively comparable to the therapeutic effects in a case of administering the antibody in 4/2/1 dosage regimen as described in the package insert of Herceptin that has been distributed after the priority date.

As aforementioned, however, the specification fails to describe extended time to disease progression or survival rate in a case of administering the antibody in 8/6/3 dosage regimen. The specification only discloses that a trough serum concentration to be maintained by the dosage regimen is at most 17 μg/ml. Even if a package insert of Herceptin (The 25th Edition) should disclose that a trough serum concentration to be maintained in 8/6/3 dosage regimen was 58.5 ± 21.6 μg/ml or 71.2 ± 23.2 μg/ml (Exhibit Ko 24, page 5, left column), the package insert was revised and distributed on December 2015, which is more than 15 years after the priority date, and the addition of efficacy has been made on November 2011. The specification has no basis to consider the description of the package insert in the determination of the significance of the effects of Invention 6. If new effects without disclosure or suggestion in the specification should be presented later, and this has significant effects comparable to the conventional technique, it is not reasonable to consider this.

(E) As aforementioned, it cannot be recognized that Invention 6 causes therapeutic effects comparable to those of Cited Invention 2-1, and thus the threefold extension of dosing interval cannot be a ground for the fact that the effects of Invention 6 are unexpected and significant comparable to Cited Invention 2-1.

C Summary

Therefore, a person ordinarily skilled in the art could have easily conceived of the configuration of Invention 6 according to Difference 2 on the basis of Cited Document 2 and the common general technical knowledge. It cannot be said that Invention 6 causes significant effects unexpected by a person ordinarily skilled in the art. Invention 6 was easily conceivable by a person ordinarily skilled in the art on the basis of Cited Invention 2-1 and common general technical knowledge. The trial decision should be rescinded due to the erroneous determination of the inventive step according to Invention 6.

(5) The inventive step of Inventions 1 to 5, 7 to 9

A Inventive step of Invention 1

There is no dispute between parties with regard to the fact that Cited Document 2 discloses Cited Invention 2-2 as shown in the aforesaid No. 2 3(3)A(A), and a Differences between Invention 1 and Cited Invention 2-2 is as shown in aforesaid No. 2, 3(3)A(B)b.

Further, in a similar manner to Invention 6, a person ordinarily skilled in the art could have easily conceived of the configuration of Invention 1 according to Difference 2 on the basis of Cited Document 2 and the common general technical knowledge. It cannot be said that Invention 1 causes significant effects unexpected by a person ordinarily skilled in the art.

Therefore, Invention 1 was easily conceivable by a person ordinarily skilled in the art on the basis of Cited Invention 2-2 and common general technical knowledge. The trial decision should be rescinded due to the erroneous determination of the inventive step according to Invention 1.

B Inventive step of Inventions 2 to 5 and 7 to 9

The trial decision determined that Inventions 2 to 5 are inventions that further confine the scope of Invention 1, and thus similarly to Invention 1, Inventions 7 to 9 are inventions that further confine the scope of Invention 6, and thus similarly to Invention 6, a person ordinarily skilled in the art could not have easily conceived of the Inventions.

As described above, however, Inventions 1 and 6 were both easily conceivable by a person ordinarilyskilled in the art. The determination of the trial decision should be rescinded in that it concluded without considering the remaining Differences that there were no grounds for requesting the trial in connection with the inventive step of Inventions 2 to 5 and 7 to 9.

(6) Therefore, the court finds the grounds 3 for rescission reasonable.

3. Conclusion

As seen above, the court finds the grounds 3 for rescission as the Plaintiffs argue reasonable and thus accepts the Plaintiffs' request, and renders a judgment as in the main text.

Intellectual Property High Court, First Division

Presiding Judge TAKABE Makiko

Judge SUGIURA Masaki

Judge KATASE Akira

Attachment

The Specification, List of Drawings and Tables

Table 2

Herceptin(R) antiErbB2 antibody for the treatment over initial eight weeks

Trough and peak serum concentration (μg/ml)

	Dose Number	n	Average value	Standard deviation	Minimum value	Maximum value
Peak Trough	1	195 195	100.3 25.0	35.2 12.7	30.7 0.16	274.6 60.7
Peak Trough	2	190 167	74.3 30.4	31.3 16.0	20.8 0.2	307.9 74.4
Peak Trough	3	167 179	75.3 33.7	26.8 17.9	16.1 0.2	194.8 98.2
Peak Trough	4	175 132	80.2 38.6	26.9 20.1	22.2 0.2	167 89.4
Peak Trough	5	128 141	85.9 42.1	29.2 24.8	27.8 0.2	185.8 148.7
Peak Trough	6	137 115	87.2 43.2	32.2 24.0	28.9 0.2	218.1 109.9
Peak Trough	7	114 137	89.7 48.8	32.5 24.9	16.3 0.2	187.8 105.2
Peak Trough	8	133	95.6	35.9	11.4	295.6

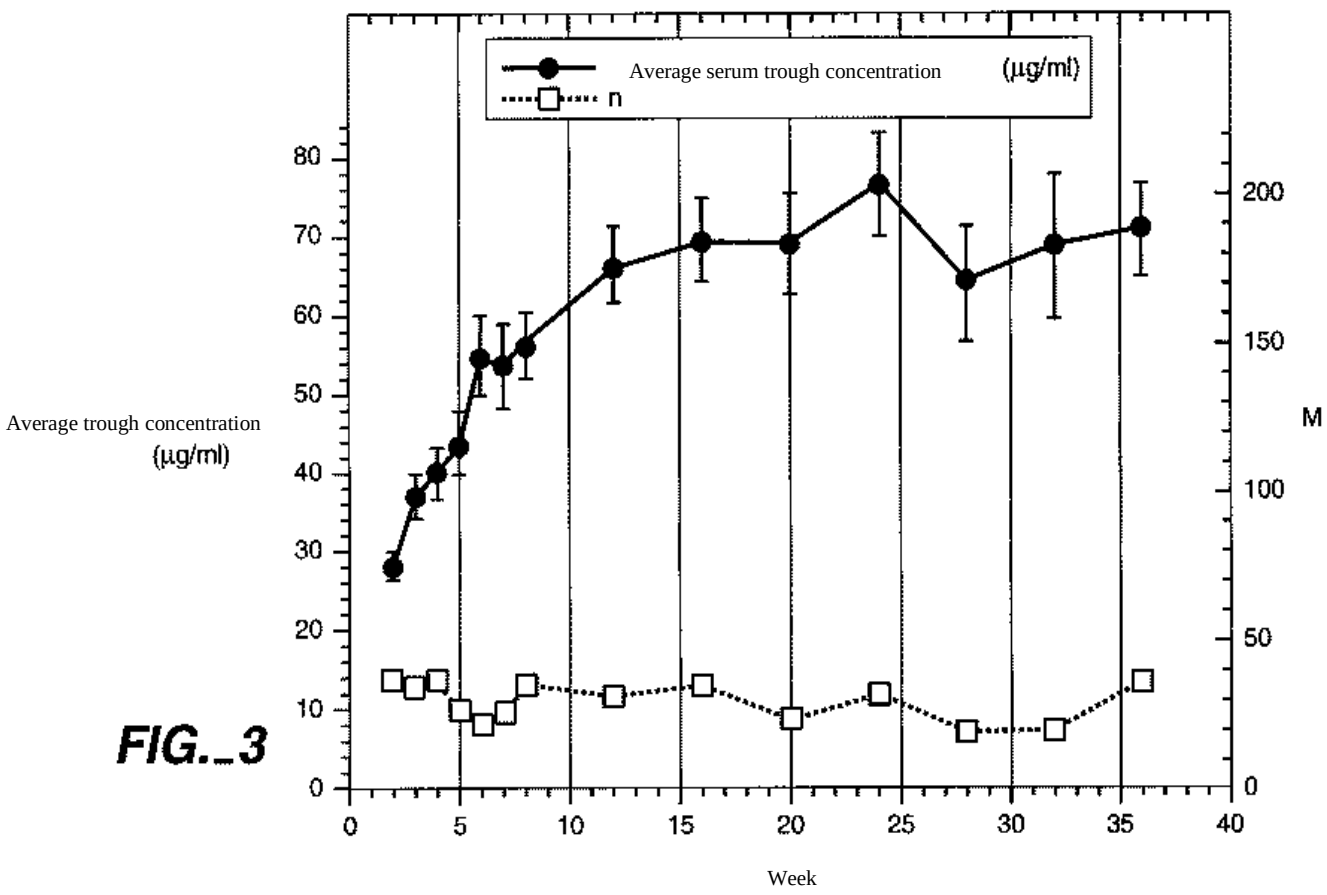
Average serum trough concentration (μg/ml)
n
Average trough concentration (μg/ml)
M
Week
0
10
20
30
40
50
60
70
80
0
50
100
150
200
0
5
10
15
20
25
30
35
40

FIG._3