Patent Right	Date	October 30, 2019	Court	Intellectual Property High Court, First Division
	Case number	2019 (Ne) 10014		
- A case in which, with regard to the scope of claims including the constituent features of "neutralizing" and "competing with an antibody", the court has comprehensively taken the recitation of the scope of claims and the description of each of the specification into account and construed the constituent features. - A case in which, with regard to the patent titled "ANTIGEN BINDING PROTEIN AGAINST PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)", the court has determined that it does not violate the support requirement and the enablement requirement. - A case in which the court has determined that it cannot be said that the injunctive relief of the production. transfer, etc. of antibody and pharmaceutical product is an abuse of right.				

Case type: Injunction

Result: Appeal Dismissed

References: Article 70, paragraph (1) and paragraph (2), Article 104-3, Article 100, paragraph (1) and paragraph (2) of the Patent Act

Number of related rights, etc.: Patent No. 5705288, Patent No. 5906333

Summary of the Judgment

1. This case is a case where Appellee, who owns two patent rights titled "ANTIGEN-BINDING PROTEIN AGAINST PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)", seeks against Appellant an injunction of the production, transfer, import, or offer to transfer of the Defendant's products and Defendant's monoclonal antibody by Appellant and a disposal of Defendant's products and Defendant's monoclonal antibody, alleging that the above Appellant's acts infringe each of the patent rights.

The judgment in prior instance ordered against Appellant an injunction of the production, transfer, import, or offer to transfer of Defendant's products and Defendant's monoclonal antibody and dismissed the remaining claims from Appellee, stating that Defendant's products and Defendant's monoclonal antibody fall within the technical scopes of Inventions 1 and 2 and Corrected Inventions 1 and 2, and none of the reasons for invalidation as Appellant alleges has a point.

Appellant filed an appeal objecting to the judgment in prior instance.

2. In summary, the court decision has dismissed the appeal, stating that Defendant's product and Defendant's monoclonal antibody fall within the technical scope of each of the Inventions, and it cannot be recognized that each of the

Inventions should be invalidated for the reasons of nonconformance to the support requirement, nonconformance to the enablement requirement, and lack of inventive step, nor is it construed that the injunctive relief is not permitted due to abuse of right.
(1) Whether or not to fall within the technical scope of each of the Inventions
A. Comprehensively taking into account the recitation of the scope of claims and the description of each of the specifications, "neutralizing" the binding of PCSK9 and LDLR in each of the Inventions is to prevent the binding of PCSK9 to LDLR, and it is recognized that "competing with an antibody" of each of the inventions is a competition between antigen-binding proteins measured by competition assay, and means the binding to the same epitope to which a reference antibody binds to PCSK9, or an overlapping epitope, or the binding to an adjacent epitope that produces a steric hindrance for the binding of reference antibody with PCSK9.

The "antibody", a basis for the competition for the binding with PCSK9 in Defendant's monoclonal antibody, further specifies reference antibody 1 of Invention 1 and reference antibody 2 of Invention 2 by an amino acid sequence of variable region, and thus fulfills both reference antibody 1 and reference antibody 2. Further, Defendant's monoclonal antibody and Defendant's product respectively fulfill the remaining constituent features of each of the Inventions.
B. Appellant alleges as follows: each of the Inventions is a functional claim specifying the invention only by a function competing with reference antibody 1 or 2, and thus the technical scope of the invention should be defined on the basis of the technical idea shown in the specific configuration that the Applicant disclosed in the specification, it should be limited to a scope within which a person ordinarily skilled in the art can perform from the description of the specification, and the technical scope of each of the Inventions is limited to a specific antibody described in the example of each of the specifications or an antibody having an amino acid sequence in which one or several amino acids at a specific position are substituted in the former antibody. Thus, Defendant's monoclonal antibody and Defendant's product having a different amino acid sequence from them respectively do not fall within the technical scope of each of the Inventions.

Setting aside the question of whether each of the Inventions should be called a so-called "functional claim", the technical scope of the patent invention must be determined on the basis of the recitation of the scope of claims, and should be construed on the basis of a technical idea disclosed therein by taking the description of the specification and drawings into account, and the Appellant's allegation should be considered as a problem of support requirement or enablement requirement. A

technical idea disclosed in each of the specifications is that an isolated monoclonal antibody competing with reference antibody 1 or 2 binds to PCSK9 in a location and/or a manner that prevents PCSK9 from binding to LDLR, blocks (neutralizes) the binding between PCSK9 and LDLR, and reduces LDL level in a subject to exert an effect of causing the decrease of serum cholesterols in a subject. Further, as aforementioned, Defendant's monoclonal antibody and Defendant's product fall within a technical scope of each of the Inventions that are construed on the basis of the above technical idea. Each of the Inventions provides an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with each of reference antibodies, and has constituent features of both blocking the binding between PCSK9 and LDLR for "neutralization" and "competing" with a reference antibody with regard to the binding with PCSK9. Further, it cannot be said that there is a description in each of the specifications that makes us believe that each of the Inventions is specified only by a function to compete with reference antibody 1 or 2. Appellant's allegation of each of the Inventions being limited to the example on the premise of that is not acceptable.

C. As described above, Defendant's monoclonal antibody and Defendant's product respectively fall within the technical scopes of Inventions 1 and 2.

(2) Nonconformance to support requirement

Each of the Inventions provides an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with reference antibody 1 or 2, and a pharmaceutical composition using the same. It can be seen that the problem lies in the provision of such novel antibody and the preparation of a pharmaceutical composition using the same that can neutralize the binding of PCSK9 and LDLR and increase the amount of LDLR, thereby resulting in a reduction in the subject's serum cholesterol level and treating or preventing or reducing the risk of the diseases associated with increased cholesterol level such as hypercholesteremia.

Each of the specifications discloses that hybridomas have been prepared by use of immunized mice produced in accordance with the description of each of the specifications, and 2441 stable hybridomas producing an antibody that binds to PCSK9 have been established by screening, and it has been found that, of these, 39 antibodies in total were subjected to an epitope binning, which resulted in 15 neutralizing antibodies not competing with 31H4 but competing with 21B12 and 7 neutralizing antibodies not competing with 21B12 but competing with 31H4. Further, each of the specifications also discloses that 21B12 and 31H4 have excellent effects of blocking the binding of PCSK9 and EGFa domain of LDLR.

21B12 is included in reference antibody 1, and 31H4 is included in reference antibody 2. Thus, it can be seen that an antibody competing with 21B12 is an antibody competing with reference antibody 1 and an antibody competing with 31H4 is an antibody competing with reference antibody 2. Consequently, it is recognized that a person ordinarily skilled in the art who read each of the specifications could recognize that, in addition to the fact confirmed as a result of the above epitope binning assay that the specific antibodies are obtained, neutralizing antibodies competing with reference antibody 1 or 2 may be obtained through a similar epitope binning assay for the above remaining antibodies obtained from the above 2441 stable hybridomas, and have an effect of causing the decrease of serum cholesterols in a subject. Furthermore, each of the specifications describes procedure of immunization program, a method of screening, and an epitope binning assay. It is recognized that based on these descriptions, a person ordinarily skilled in the art could recognize that neutralizing antibodies competing with reference antibody 1 or 2 might be obtained in addition to neutralizing antibodies competing with the reference antibody specifically described in each of the specifications, by repetitively implementing a series of procedures from the start.

It is recognized that based on the above, a person ordinarily skilled in the art can obtain an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with reference antibody 1 or 2 on the basis of the description of each of the specifications, and thus a novel antibody of monoclonal antibody of each of the Invention is provided, and one can recognize the fact that a pharmaceutical composition of each of the Inventions using them may treat or prevent or reduce the risk of the diseases associated with increased cholesterol level such as hypercholesteremia. It is thus recognized that each of the Inventions conforms to the support requirement.

(3) Nonconformance to enablement requirement

It can be seen from the description of each of the specifications that an antibody and a pharmaceutical composition of each of the Inventions may be produced and used, and it can be said that the description of Detailed Description of Inventions in each of the specifications definitely and sufficiently describes to the extent that allows a person ordinarily skilled in the art to implement each of the Inventions. Thus, it is recognized that each of the Inventions conforms to the enablement requirement.

(4) Propriety of injunctive relief

A. Appellant alleges that Appellant does not produce Defendant's products, nor

does it produce, import, transfer, and offer to transfer its raw material of Defendant's monoclonal antibody; however, it cannot be ruled out that Appellant might possibly produce Defendant's product or transfer Defendant's monoclonal antibody following the import or production of Defendant's monoclonal antibody, and thus it must be said that Appellant is likely to produce Defendant's product or conduct each of an act of production, import, transfer, and offer to transfer of Defendant's monoclonal antibody, and the necessity of injunction is recognized.

B. Appellant alleges that Appellee's claim for injunction corresponds to the abuse of rights since the injunction of the production and transfer, etc. of Defendant's product and Defendant's monoclonal antibody causes patients currently administered or to be administered Defendant's product to have severe health risk or anxiety for future therapy. In the field of pharmaceutical products, there might be the case where a right to seek injunction should be limited from a viewpoint of public interests; however, it cannot be concluded that an injunction of the production, transfer, etc. of infringing products should not be permitted, without establishing concrete facts, for a simple reason that it is desirable for patients to have a selectable option.

Judgment rendered on October 30, 2019
2019 (Ne)10014 Appeal case of seeking injunction against patent infringement
(court of Prior Instance: Tokyo District Court, 2017 (Wa) 16468)
Date of conclusion of oral argument: July 3, 2019

Judgment

Appellant: Sanofi Incorporated

Appellee: Amgen Incorporated

Main text

1. The appeal shall be dismissed.

2. Appellant shall bear the cost of the appeal.

Facts and reasons

No. 1 Gist of the Appeal

1. A part where the Appellant was defeated in the prior instance judgment shall be reversed.

2. All of the Appellee's claims according to the above rescinded part shall be dismissed.

3. Appellee shall bear the court costs for both the first and second instances.

No. 2 Outline of the case (unless otherwise specified, abbreviated names are in accordance with those of the judgment in prior instance).

1. This case is a case where Appellee, who owns two patent rights titled "ANTIGEN-BINDING PROTEIN AGAINST PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)", seeks against Appellant an injunction of the production, transfer, import, or offer to transfer of the Defendant's products and Defendant's monoclonal antibody by Appellant and a disposal of Defendant's products and Defendant's monoclonal antibody, alleging that the above Appellant's acts infringe each of the patent rights.

The judgment in prior instance ordered against Appellant an injunction of the production, transfer, import, or offer to transfer of Defendant's products and Defendant's monoclonal antibody and dismissed the remaining claims from Appellee, stating that Defendant's products and Defendant's monoclonal antibody fall within the technical scopes of the Inventions 1 and 2 and Corrected Inventions 1 and 2, and none

of the reasons for invalidation as Appellant alleges has a point.

Appellant filed an appeal objecting to the judgment in prior instance.

2. Facts used as premise

Except for the following amendment, "Facts and reasons" of the judgment in prior instance, No. 2-1 is maintained. Thus, this is incorporated by reference.

(1) Page 5, lines 12 to 15 of the judgment in prior instance shall be modified as follows:

"A Request for correction

In the case of request for invalidation trial of Patent 1 on May 8, 2017 (the case of Invalidation Trial No. 2016-800004, hereinafter referred to as 'Case 1 for invalidation trial') Appellee has made a request for correction to correct Claims 1 and 9 and delete Claims 2 to 4 from a group of claims consisting of Claims 1 to 4 and 9 of the scope of claims, and to delete a group of claims consisting of Claims 5 to 8 (Exhibit Ko 11-1, hereinafter referred to as 'Correction 1'). In the case of request for invalidation trial of Patent 2 (the case of Invalidation Trial No. 2016-800066, hereinafter referred to as 'Case 2 for invalidation trial') Appellee has made a request for correction to correct Claims 1 and 5 and delete Claim 2 from a group of claims consisting of Claims 1, 2, and 5 of the scope of claims, and delete a group of claims consisting of Claims 3 and 4 (Exhibit Ko 11-2, hereinafter referred to as 'Correction 2').

The Japan Patent Office accepted Correction 1 with respect to Case 1 for invalidation trial on August 2 of the same year, and made a decision to the effect that the trial for the inventions according to Claims 1 and 9 was groundless, and the trial for Claims 2 to 8 should be dismissed, and accepted Correction 2 with respect to Case 2 for invalidation trial, and the trial for the inventions according to Claims 1, 5 was groundless, and the trial for Claims 2 to 4 should be dismissed.

On December 8, 2017, Appellant filed a suit against trial decision made by the JPO seeking a rescission of a part according to Claims 1 and 9 of Patent 1 in the trial decision with respect to Case 1 for invalidation trial (Japan Patent Office 2017(Gyo-Ke)10225, hereinafter referred to as 'Suit 1 against trial decision made by JPO') and filed a suit against trial decision made by JPO seeking a rescission of a part according to Claims 1 and 5 of Patent 2 in the trial decision with respect to Case 2 for invalidation trial (2017(Gyo-Ke)10226, hereinafter referred to as 'Suit 2 against trial decision made by JPO').

On December 27, 2018 the Intellectual Property High Court made a court decision to dismiss Appellant's claims for both Suits 1 and 2 against trial decision

made by the JPO, and Appellant has petitioned for acceptance of final appeal.

B. Patent 1 after correction"

(2) "B. Patent 2" of the judgment in prior instance, page 6, line 3 is modified to "C. Patent 2 after correction".

(3) Page 6, lines 16 to 26 of the judgment in prior instance shall be modified as follows:

"(5) Hereinafter, 'an antibody comprising: a heavy chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 368, 175, and 180; and a light chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 158, 162, and 395' of Invention 1 (Constituent Feature 1B) is referred to as 'reference antibody 1'. 'An antibody comprising: a heavy chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 247, 256, and 265; and a light chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 222, 229, and 238' of Invention 2 (Constituent Feature 2) is referred to as 'reference antibody 2'. 'An antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 49; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 23' of Corrected Invention 1 (constituent feature 1B') is referred to as 'reference antibody 1'. 'An antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 67; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 12' of Corrected Invention 2 (constituent feature 2B') is referred to as 'reference antibody 2'.

Further, in some cases, Invention 1 and Invention 2 are collectively referred to as 'each of the Inventions', and Corrected Invention 1 and Corrected Invention 2 are collectively referred to as 'each of the Corrected Inventions'."

3. Issues

(1) Whether or not to fall within the technical scopes of each of the Inventions and each of the Corrected Inventions

Whether Defendant's products and Defendant's monoclonal antibody fall within the technical scopes of each of the Inventions and each of the Corrected Inventions.

(2) Presence or absence of reasons for invalidation

Whether each of the Patents should be invalidated for the reasons of the following A to D.

A. Nonconformance to support requirement

B. Nonconformance to enablement requirement

C. Lack of inventive step on the basis of the invention described in Thomas A. Lagace et al., "Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice", The Journal of Clinical Investigation, Vol. 116, No. 11, pp. 2995-3005 (Exhibit Otsu 1, published on November 2006)

D. Yue-Wei Qian et al., "Secreted PCSK9 downregulates low density lipoprotein receptor through receptor-mediated endocytosis" Journal of Lipid Research, Vol. 48, pp. 1488-1498 (Exhibit Otsu 27, published on April 2007, hereinafter referred to as "Exhibit Otsu 27 Document"). (Issues added in this appellate instance)

(3) Propriety of injunctive relief

A. Necessity of injunction

B. Abuse of rights (Issues added in this appellate instance)

(omitted)

No. 4 Judgment of this court

The court has also determined that Defendant's monoclonal antibody falls within a technical scope of Inventions 1-1 and 2-1, Defendant's product falls within a technical scope of Inventions 1-2 and 2-2, and further each of the Patents should be invalidated by a trial for patent invalidation. The reason is set forth as below.

1. The Invention

(1) The description of each of the specifications

Except for the following amendment to the description of each of the specifications, the description from page 22, line 22 to page 36, line 7 of the judgment in prior instance is maintained. Thus, this is incorporated by reference.

A. Following "has the following description" of page 22, line 23 of the judgment in prior instance, "(See the attachment with regard to Table 2 and Table 3 cited by the following description)" shall be added, and Table 2 and Table 3 shall be attached to the attachment.

B. Add as below with a carriage return to the end of page 29, line 15 of the judgment in prior instance:

" 'Antigen binding region' means a protein, or a portion of a protein, that specifically binds a specified antigen (e.g., a paratope). For example, that portion of an antigen binding protein that contains the amino acid residues that interact with an antigen and confer on the antigen binding protein its specificity and affinity for the

antigen is referred to as 'antigen binding region'. An antigen binding region typically includes one or more 'complementary binding regions' ('CDRs'). Certain antigen binding regions also include one or more 'framework' regions. A 'CDR' is an amino acid sequence that contributes to antigen binding specificity and affinity. 'Framework' regions can aid in maintaining the proper conformation of the CDRs to promote binding between the antigen binding region and an antigen. Structurally, framework regions can be located in antibodies between CDRs. Examples of framework and CDR regions are shown in FIGs. 2A-3D, 3CCC-JJJ, and 15A-15D. ..."

"The variable regions typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, (also called complementarity determining regions or CDRs). The CDRs from the two chains of each pair typically are aligned by the framework regions, which can enable binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. ..." (paragraphs [0123], [0127])

"The term 'light chain' includes a full-length light chain and fragments thereof having a sufficient variable region sequence to confer binding specificity. A full-length light chain includes a variable region domain, V_L, and a constant region domain, C_L. The variable region domain of the light chain is at the amino-terminus of the polypeptide. Light chains include κ chains and λ chains."

"The term 'heavy chain' includes a full-length heavy chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length heavy chain includes a variable region domain, V_H, and three constant region domains, C_H1, C_H2, and C_H3. The V_H domain is at the amino-terminus of the polypeptide, and the C_H domains are at the carboxyl-terminus, with the C_H3 being closest to the carboxy-terminus of the polypeptide. Heavy chains can be of any isotype, including IgG (including IgG1, IgG2, IgG3, and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM, and IgE." (paragraphs [0132] to [0133])

C. Add as below with a carriage return to the end of page 32, line 23 of the judgment in prior instance:

" 'Antigen-binding protein against PCSK9

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein (Horton et al, 2007; Seidah and Prat, 2007). PCSK9 is a prohormone-proprotein convertase in the subtilisin (S8) family of serine proteases (Seidah et al, 2003). ... The structure of the PCSK9 protein has recently been solved by two

groups (...). PCSK9 includes a signal sequence, an N-terminal prodomain, a subtilisin-like catalytic domain, and a C-terminal domain.' (paragraph [0154])"

D. Add as below with a carriage return to the end of page 33, line 22 of the judgment in prior instance:

" '... In some embodiments, ABP binds to any one of epitope to be bonded by an antibody discussed in the specification. In some embodiments, this can be measured by competing assay between an antibody disclosed in the specification and the other antibody. ...' (paragraph [0157])

'Specific examples of some of the variable regions of the light and heavy chains of the antibodies that are provided and their corresponding amino acid sequences are summarized in TABLE 2.'

'Again, each of the exemplary variable heavy chains listed in Table 2 can be combined with any of the exemplary variable light chains shown in Table 2 to form an antibody. Table 2 shows exemplary light and heavy chain pairings found in several of the antibodies disclosed herein. ...' (paragraphs [0170], [0172])"

E. Add as below with a carriage return to the end of page 34, line 6 of the judgment in prior instance:

" 'In some embodiments, ABP 21B12 binds to an epitope including residues 162-167 (e.g., residues D162-E167 of SEQ ID NO: 1). ...'
(paragraph [0268])"

F. Add as below with a carriage return to the end of page 36, line 7 of the judgment in prior instance:

" '(Example 3) Selection of PCSK9 antibody ... The selection of antibodies was based on binding data and inhibition of PCSK9 binding to LDLR and affinity. ...' (paragraph [0325])

'Large Scale Receptor Ligand Blocking Screen To screen for the antibodies that block PCSK9 binding to LDLR, an assay was developed using the D374Y PCSK9 mutant.... The screen identified 384 antibodies that blocked the interaction between PCSK9 and the LDLR well, 100 antibodies blocked the interaction strongly....' (paragraph [0332])

'(Example 11) Efficacy of 31H4 and 21B12 for Blocking D374Y PCSK9/LDLR Binding

This example provides the IC50 values for two of the antibodies in blocking PCSK9 D374Y's ability to bind to LDLR....' (paragraph [0377])"

(2) According to the description of each of the specifications of the above (1), it is recognized that each of the Inventions is summarized as set forth below.

Specifically, PCSK9 (Proprotein convertase subtilisin kexin type 9) binds to LDLR (low density lipoprotein receptor) and interacts to be incorporated into liver cells together with LDLR and decrease LDLR level in liver, and further decrease an amount of LDLR available for the binding to LDL on the cell surface (extracellular) to increase an amount of LDL in a subject ([0002], [0003], [0071]). An isolated monoclonal antibody "competing" with reference antibody 1 (Invention 1) or reference antibody 2 (Invention 2) is a neutralization antigen binding protein (neutralizing ABP) that binds to PCSK9 in a location and/or a manner that prevents PCSK9 from binding to LDLR and blocks or reduces and "competitively neutralizes" the interaction (binding) between PCSK9 and LDLR ([0138], [0140], [0155], [0157], [0261], [0262], [0269], Table 2). This neutralizing ABP against PCSK9 can neutralize the binding of PCSK9 and LDLR and increase the amount of LDLR, thereby decreasing the amount of serum LDL in a subject, resulting in a reduction in the subject's serum cholesterol level and this effect may treat or prevent or reduce the risk of the diseases associated with increased cholesterol level such as hypercholesteremia, and thus may be therapeutically beneficial ([0155], [0270], [0271], [0276]).

2. Issue (1) (Whether or not to fall within the technical scope of each of the Inventions)

(1) Construction of each of the Inventions

A. Meaning of "neutralization"

The scope of claims of each of the Patents (Claim 1) describes that "capable of neutralizing the binding of PCSK9 and LDLR proteins" (constituent features 1A, 2A).

Further, each of the specifications describes that "the term 'neutralizing antigen binding protein' or 'neutralizing antibody' refers to an antigen binding protein or antibody, respectively, that binds to a ligand and prevents or reduces the biological effect of that ligand.... In the case of PCSK9 antigen binding proteins, such a neutralizing molecule can diminish the ability of PCSK9 to bind the LDLR.... the antibodies or antigen binding proteins neutralize by binding to PCSK9 and preventing PCSK9 from binding to LDLR (or reducing the ability of PCSK9 to bind to LDLR)." ([0138]). In addition, it describes in Examples "(Example 3) Selection of PCSK9 Antibodies ... Selection of antibodies was based on binding data and inhibition of PCSK9 binding to LDLR and affinity." ([0325]), "Large Scale Receptor Ligand Blocking Screen To screen for the antibodies that block PCSK9 binding to LDLR, an assay was developed using the D374Y PCSK9 mutant .... The screen identified 384 antibodies that blocked the interaction between PCSK9 and the LDLR well,

among which 100 antibodies blocked the interaction strongly" ([0332]), "(Example 11) Efficacy of 31H4 and 21B12 for Blocking D374Y PCSK9/LDLR Binding This example provides the IC50 values for two of the antibodies in blocking PCSK9 D374Y's ability to bind to LDLR...." ([0377]).

Consequently, it can be seen that "neutralizing" the binding of PCSK9 and LDLR is to prevent the binding of PCSK9 and LDLR protein or block the binding of PCSK9 to LDLR.

Therefore, it is recognized that "neutralizing" the binding of PCSK9 and LDLR in each of the Inventions is to prevent the binding of PCSK9 to LDLR.

B. Meaning of "competition"

The scope of claims of each of the Patents (Claim 1) recites that "competing" with reference antibody 1 or 2 "for binding with PCSK9". This suggests the competition with a specific reference antibody for binding with PCSK9. This does not describe the meaning of "competing with an antibody".

Further, each of the specifications discloses that "The term 'compete' when used in the context of antigen binding proteins (e.g., neutralizing antigen binding proteins or neutralizing antibodies) that compete for the same epitope means competition between antigen binding proteins as determined by an assay in which the antigen binding protein ... being tested prevents or inhibits (e.g., reduces) specific binding of a reference antigen binding protein (e.g., a ligand, or a reference antibody) to a common antigen (e.g., PCSK9 ...). ... Antigen binding proteins identified by competition assay (competing antigen binding proteins) include antigen binding proteins binding to the same epitope as the reference antigen binding proteins and antigen binding proteins binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen binding protein for steric hindrance to occur." ([0140]), "the neutralizing ABP binds to PCSK9 in a location and/or manner that prevents PCSK9 from binding to LDLR. Such ABPs can be specifically described as 'competitively neutralizing' ABPs." ([0155]), "In some embodiments, ABP binds to any one of epitope to be bonded by an antibody discussed in the specification. In some embodiments, this can be measured by competing assay between an antibody disclosed in the specification and the other antibody." ([0157]). In addition, it describes in Examples that "there is provided antigen binding proteins that compete with one of the exemplified antibodies ... binding to the epitope described herein for specific binding to PCSK9. Such antigen binding proteins can also bind to the same epitope as one of the herein exemplified antigen binding proteins, or an overlapping epitope." ([0269]).

Comprehensively taking into account the recitation of the scope of claims and the description of each of the specifications, it is recognized that "competing with an antibody" of each of the inventions is a competition between antigen-binding proteins measured by competition assay, and means the binding to the same epitope to which a reference antibody binds to PCSK9, or an overlapping epitope, or the binding to an adjacent epitope that produces a steric hindrance for the binding of reference antibody with PCSK9.

In addition, Encyclopedia of Immunology, 2nd Edition describes that "competition inhibition test" is "also referred to as competition inhibitory test. It may include, for example, a type of inhibition in which something competes with an antigen molecule to compete for a site of an antibody molecule, and a type of inhibition in which something competes with an antibody molecule to compete for an antigen determinant of an antigen molecule". Encyclopedia of Biochemistry, 4th Edition describes that "competitive inhibition" is "also referred to as antagonistic inhibition or competition inhibition. Catalytic activity of enzymes may be frequently subjected to reversible inhibition by various compounds. The inhibition of enzymatic activity has various forms. Particularly, a type of inhibition in which an inhibitor molecule competes with a substrate molecule to compete for a substrate-binding site is a competitive inhibition". "Competition" is used in the sense of competing for a binding site. As aforementioned, however, it is obvious in each of the specifications that "competing" means a competition between antigen-binding proteins measured by competition assay, and is not limited to a case of competing for a same binding site, but includes the binding to an adjacent epitope that produces a steric hindrance for the binding between the reference antibody and PCSK9.

(2) Fulfillment of the constituent feature of each of the inventions in question

A. Constitution of Defendant's monoclonal antibody and Defendant's products

Obviously, Appellant does not object to the fact that Defendant's monoclonal antibody is

"c. an isolated monoclonal antibody

a. capable of inhibiting the binding of PCSK9 and LDLR protein,

b. competing with the antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 49; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 23 for binding with PCSK9,

b'. competing with the antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 67; and a light

chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 12 for binding with PCSK9."
and further Defendant's product is
"d. A pharmaceutical composition comprising
c. an isolated monoclonal antibody
a. capable of inhibiting the binding of PCSK9 and LDLR protein,
b. competing with the antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 49; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 23 for binding with PCSK9,
b'. competing with the antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 67; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 12 for binding with PCSK9."

B. Fulfillment of the constituent feature of the invention in question

(A) Defendant's monoclonal antibody binds to PCSK9 and inhibits the binding of PCSK9 to LDLR (the above a), and thus "neutralizes" the binding of PCSK9 and LDLR, and fulfills the constituent features 1A and 2A.

(B) In Defendant's monoclonal antibody, an antibody that can be a basis for the competition for binding with PCSK9 is an antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 49; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 23 (the above b) and an antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 67; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 12 (the above b').

As aforementioned, "competing" means the binding to the same epitope to which a reference antibody binds to PCSK9, or an overlapping epitope, or the binding to an adjacent epitope that produces a steric hindrance for the binding of the reference antibody with PCSK9. Thus, it becomes a point of issue as to whether or not "antibody" which is the basis for competition for binding with PCSK9 fulfills the reference antibody of each of the Inventions in Defendant's monoclonal antibody.

The reference antibody of Invention 1 is reference antibody 1 (an antibody comprising: a heavy chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 368, 175, and 180; and a light chain

comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 158, 162, and 395). The reference antibody of Invention 2 is reference antibody 2 (an antibody comprising: a heavy chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 247, 256, and 265; and a light chain comprising CDR1, 2, and 3 respectively consisting of the amino acid sequences of SEQ ID NOS. 222, 229, and 238). The above antibody b further limits reference antibody 1 to an amino acid sequence in a variable region. The above antibody b' further limits reference antibody 2 to an amino acid sequence in a variable region (No issue between parties), thus it is recognized that antibody b fulfills reference antibody 1, and antibody b' fulfills reference antibody 2.

Therefore, Defendant's monoclonal antibody competes with reference antibody 1 and reference antibody 2 for binding with PCSK9, and thus fulfills the constituent features 1B and 2B.

(C) Defendant's monoclonal antibody is an isolated monoclonal antibody from which impurities derived from any production step are sufficiently removed in the production step of Defendant's product (the above c), and fulfills the constituent features 1C and 2C.

(D) Defendant's product is a pharmaceutical product composition comprising Defendant's monoclonal antibody (the above d), and thus fulfills the constituent features 1D and 2D in addition to the constituent features 1A to C and 2A to C.

(E) As described above, Defendant's monoclonal antibody fulfills all the constituent features of Inventions 1-1 and 2-1, and Defendant's products fulfill all the constituent features of Inventions 1-2 and 2-2.

(3) Appellant's allegation

A. Appellant alleges that each of the Inventions is a functional claim that specifies the invention only by a function to compete with reference antibody 1 or 2, and in such a functional claim, if it should be construed that the entire constitution capable of causing the function and effect should fall within a technical scope, the one having a technical concept different from that disclosed in the specification might be encompassed into the technical scope of the invention, which results in the protection by a patent right beyond what the Applicant has invented, and thus when it comes to a functional claim, the technical scope of the invention should be defined on the basis of the technical idea shown in the specific configuration that the Applicant disclosed in the specification by taking into account the description of the Detailed Description of the Invention of the specification in addition to the recitation of the claims, and thus a functional claim should be narrowly construed to have a scope within which a

person ordinarily skilled in the art can perform from the description of the specification. Further, Appellant alleges that a scope where a person ordinarily skilled in the art can perform from the description of the specification is limited to a specific antibody described in the example of each of the specifications or an antibody having an amino acid sequence in which one or several amino acids at a specific position are substituted in the former antibody, and thus the technical scope of each of the inventions is limited to each of the above antibody or an amino acid sequence in which one or several amino acids at a specific position is substituted in the antibody, Defendant's monoclonal antibody and Defendant's product having a different amino acid sequence from them respectively do not fall within a technical scope of each of the Inventions.

Setting aside the question of whether each of the Inventions should be called a so-called "functional claim", the technical scope of the patent invention must be determined on the basis of the recitation of the scope of claims, and should be construed on the basis of a technical idea disclosed therein by taking the description of the specification and drawings into account, and the Appellant's allegation should be considered as a problem of support requirement or enablement requirement. A technical idea disclosed in each of the specifications is that an isolated monoclonal antibody competing with reference antibody 1 or 2 binds to PCSK9 in a location and/or a manner that prevents PCSK9 from binding to LDLR, blocks (neutralizes) the binding between PCSK9 and LDLR, and reduces LDL level in a subject to exert an effect of causing the decrease of serum cholesterols in a subject. Further, as aforementioned, Defendant's monoclonal antibody and Defendant's product fall within a technical scope of each of the Inventions that are construed on the basis of the above technical idea.

Each of the Inventions provides an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with each of reference antibodies, and has constituent features of both blocking the binding between PCSK9 and LDLR for "neutralization" (constituent features 1A, 2A) and "competing" with a reference antibody for binding with PCSK9 (constituent features 1B, 2B). Further, it cannot be said that there is a description in each of the specifications that makes us believe that each of the Inventions is specified only by a function to compete with reference antibody 1 or 2. Appellant's allegation of each of the Inventions being limited to the example on the premise of that is not acceptable.

Further, each of the Inventions is not specified by amino acid sequence. Thus, there is no reason to construe as being limited to a specific antibody described in each

of the specifications or an antibody having an amino acid sequence in which one or several amino acids are substituted at a specific position in the former antibody.

Furthermore, each of the specifications describes: the production of an immunized mouse in compliant with the procedure and schedule of an immunization program; the production of hybridoma for which an immunized mouse is used; and a method of screening and epitope binning assay for identification of antibody that strongly blocks the binding of PCSK9 and LDLR that competes with reference antibody 1 or 2 (the below-mentioned 3(2)). It can be recognized from these descriptions that a neutralizing antibody competing with reference antibody 1 or 2 may be obtained by repetitively implementing a series of procedures in addition to the neutralizing antibodies competing with a reference antibody specifically described in each of the specifications, and that the result of the above epitope binning assay has confirmed that 15 specific antibodies of the Invention 1 and 7 specific antibodies of the Invention 2 are obtained, and neutralizing antibodies competing with reference antibody 1 or 2 may be obtained through a similar epitope binning assay for the above remaining antibodies obtained from 2441 stable hybridomas, as per the below-mentioned 3, 4.

Consequently, it cannot be said that a scope of the invention within which a person ordinarily skilled in the art could implement from the description of each of the specifications is limited to a specific antibody described in each of the specifications or an antibody having an amino acid sequence in which one or several amino acids are substituted at a specific position in the former antibody, and the Appellant's allegation is unacceptable also in this point.

B. Appellant alleges that one could not read a technical idea that an antibody competing with reference antibody 1 or 2 can neutralize the binding of PCSK9 and LDLR from each of the specifications, nor can it be inferred from antibodies in only three groups or two groups described in the examples of each of the specifications that an enormous number of antibodies competing with reference antibody 1 or 2 are all PCSK9-LDLR binding neutralizing antibodies.

As per the aforesaid A, however, each of the specifications discloses a technical idea that an isolated monoclonal antibody competing with reference antibody 1 or 2 binds to PCSK9 in a location and/or a manner that prevents PCSK9 from binding to LDLR, blocks (neutralizes) the binding between PCSK9 and LDLR, and reduces LDL level in a subject to exert an effect of causing the decrease of serum cholesterols in a subject. There is a disclosure that a neutralizing antibody competing with reference antibody 1 or 2 may be obtained by repeatedly carrying out

a series of procedures described, in addition to the neutralizing antibodies competing with reference antibody specifically described in each of the specifications. Thus, neutralizing antibody competing with reference antibody 1 or 2 is not limited to three groups or two groups described in the examples of each of the specifications.

Further, Invention 1 has constituent features of being PCSK9-LDLR binding neutralizing antibody and being an antibody competing with reference antibody 1, and Invention 2 has constituent features of being PCSK9-LDLR binding neutralizing antibody and being an antibody competing with reference antibody 2. Therefore, first of all, one competing with reference antibody 1 or 2 but which is not a PCSK9-LDLR binding neutralizing antibody does not fall within a technical scope of Invention 1. Thus, the Appellant's allegation is not reasonable.

C. Appellant alleges that an antibody competing with reference antibody 1 or 2, which is a specific example of PCSK9-LDLR binding neutralizing antibody in each of the specifications, only binds to LDLR binding site on a surface of PCSK9 with its part being overlapped, Defendant's monoclonal antibody is an antibody (EGFa mimic) that recognizes the most part of amino acids on PCSK9 that LDLR recognizes, and thus Defendant's monoclonal antibody and Defendant's product do not fall within the technical scopes of each of the Inventions.

However, each of the Inventions is not specified by a binding site on PCSK9 that an antibody recognizes. Thus, even if the example disclosed in each of the specifications differs from Defendant's monoclonal antibody in their binding site on PCSK to be recognized, it cannot be said to not fall within a technical scope of each of the Inventions, and the Appellant's allegation is not reasonable.

D. Therefore, none of the Appellant's allegation is acceptable.

(4) In addition, both Correction 1 and Correction 2 had not yet been made final and binding as of the conclusion of oral proceeding. In view of the nature of the case, a consideration is given as to whether or not to fall within a technical scope of each of the Corrected Invention of Defendant's monoclonal antibody and Defendant's product.

Constituent features 1A, 1C, and 1D of the Corrected Invention 1 are identical to Constituent features 1A, 1C, and 1D of Invention 1, and Constituent features 2A, 2C, and 2D of Corrected Invention 2 are identical to Constituent features 2A, 2C, and 2D of Invention 2, respectively. Thus, Defendant's monoclonal antibody and Defendant's product fulfill Constituent features 1A, 2A, 1C, and 2C. Further, Defendant's product fulfills Constituent features 1D and 2D.

In Defendant's monoclonal antibody, an antibody that can be a basis for the

competition for binding with PCSK9 is "an antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 49; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 23" (the above b) and "an antibody comprising: a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 67; and a light chain comprising a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 12" (the above b'). The above b is identical to reference antibody 1' and the above b' is identical to reference antibody 2'. It is thus recognized that Defendant's monoclonal antibody and Defendant's product fulfill the constituent features 1B' and 2B'.

As described above, Defendant's monoclonal antibody fulfills all the constituent features of Corrected Inventions 1-1 and 2-1, and Defendant's products fulfill all the constituent features of Corrected Inventions 1-2 and 2-2.

(5) Summary

As described above, Defendant's monoclonal antibody falls within the technical scopes of Inventions 1-1 and 2-1 and Corrected Inventions 1-1 and 2-1, and Defendant's products fall within the technical scopes of Inventions 1-2 and 2-2 and Corrected Inventions 1-2 and 2-2.

3. Issues (2) A (Violation of Support Requirement)

(1) Each of the specifications has the following description with regard to each of the Inventions (see the attachment for Table 8.3, Table 37.1 cited in the following description).

A. PCSK9 (Proprotein convertase subtilisin kexin type 9) is a serine protease that binds to LDLR (low density lipoprotein receptor) and interacts to be incorporated into liver cells together with LDLR and decrease LDLR level in the liver, and further decrease an amount of LDLR available for the binding to LDL on a cell surface (extracellular) to increase an amount of LDL in a subject ([0002], [0003], [0071]).

The term "neutralizing antibody" represents an antibody that binds to a ligand and prevents or reduces the biological effects of the ligand. In the anti-PCSK9 antibody, it involves neutralization by prevention of the binding of PCSK9 and LDLR, and neutralization by prevention of PCSK9-mediated decomposition of LDLR without preventing the binding of PCSK9 and LDLR ([0138]).

The term "competing" means the competition between antibodies determined by various assays that measure the degree of a test antibody preventing or inhibiting a specific binding of the reference antibody to an antigen. An antibody identified by a competitive assay includes an antibody binding to an epitope identical to the reference

antibody, and an antibody binding to an adjacent epitope sufficiently close to interfere sterically with the binding of the reference antibody to the epitope ([0140]).

The term "epitope" is a region of an antigen that is bound by an antibody, and when the antigen is a protein, includes specific amino acids that directly contact the antibody ([0142]).

B. An isolated monoclonal antibody "competing" with an antibody ("21B12") comprising: a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 49; and a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 23, an isolated monoclonal antibody "competing" with an antibody ("31H4") comprising: a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO. 67; and a light chain variable region consisting of the amino acid sequence of SEQ ID NO. 12 is a neutralization antigen binding protein (neutralizing ABP) that binds to PCSK9 in a location and/or a manner that prevents PCSK9 from binding to LDLR and blocks, reduces and "competitively neutralizes" the interaction (binding) between PCSK9 and LDLR. ([0138], [0140], [0155], [0269], Table 2).

Neutralizing ABP against PCSK9 can neutralize the binding of PCSK9 and LDLR and increase the amount of LDLR, thereby decreasing the amount of serum LDL in a subject, resulting in a reduction in the subject's serum cholesterol level, and this effect may treat or prevent or reduce the risk of the diseases associated with increased cholesterol level such as hypercholesteremia, and thus may be therapeutically beneficial ([0066], [0155], [0270], [0271], [0276]).

C. A human PCSK9 antigen was injected 11 times to mice in two groups containing human immunization globulin gene to prepare immunized mice and select mice (10 mice) that produce an antibody specific to PCSK9 according to a procedure and schedule of an immunization program described in Table 3 (Example 1, [0312], [0313], [0320], Table 3).

Hybridomas producing antigen binding proteins to PCSK9 were produced by use of these selected immunized mice (Example 2, [0322] to [0324]), a total of 3104 antigen specific hybridomas were obtained by "Primary Screen" by ELiSA with a capture sample of biotinylated-PCSK9, without a V5 tag, binding to a plate coated with neutravadin (Example 3, [0325] to [0328]).

The 3000 positives in total were rescreened from the above hybridomas obtained by "Primary Screen" and further the 2441 positives in total were then rescreened ("Confirmatory Screen") to confirm that stable hybridomas were established, and then it was confirmed that 579 antibodies could bind to both human

and mouse PCSK9 by "mouse cross-reactivity screening" ([0329], [0330]). Furthermore, "large scale receptor ligand blocking screening" was implemented for screening antibody that blocks the binding of PCSK9 to LDLR, identifying 384 antibodies that strongly blocked the interaction between PCSK9 and the LDLR well, among which 100 antibodies blocked the binding interaction of PCSK9 and LDLR by 90% or more ([0332]).

For the 384 member subset of neutralizers (blockers) identified in this manner, "a receptor ligand binding assay for a subset of blockers" was implemented, and 85 antibodies blocking the interaction between PCSK9 mutant enzyme and LDLR by 90% were identified ([0333], [0334]).

Identified on the basis of the results of these assays, several hybridoma lines producing antibodies with desired interactions with PCSK9 included a reference antibody (21B12, 31H4) ([0336], Table 2), which is a neutralizing antibody that strongly blocks the binding of PCSK9 and LDLR (Example 11, [0138], [0377], [0378]).

D. From 32 antibodies in Table 2 (several hybridoma lines that produce an antibody having a desired interaction with PCSK9), 27B2, 13H1, 13B5, and 3C4 are non-neutralizing antibodies, and 3B6, 9C9, and 31A4 are weak neutralizing antibodies, and the others (including a reference antibody) are strong neutralizing antibodies ([0138], [0336]).

According to the result of epitope binning for the above 32 antibodies, the ones competing with 21B12 (bin 1) total 19, and the ones competing with 31H4 (bin 3) total 7. They are mutually exclusive. One was identified as competing with both 21B12 and 31H4 (bin 2), and one was identified as competing with neither 21B12 nor 31H4 (bin 4) (Example 10, [0373], [0494], Table 8.3).

In addition to the above set of Example 10, according to the result of epitope binning implemented for the other set (39 antibodies in total), the ones not competing with 31H4 but competing with 21B12 (bin 1) total 19, and the ones competing with both 21B12 and 31H4 (bin 2) total 3. The ones not competing with 21B12 but competing with 31H4 (bin 3) total 10. Further, it has been confirmed that 16 out of the antibodies included in BIN 1 are antibodies listed in Table 2, and of these, 15 except for 27B12 antibody are neutralizing antibodies, and 7 out of the antibodies included in BIN 3 are antibodies listed in Table 2 and are neutralizing antibodies (Example 37, [0138], [0489] to [0495], Table 37.1).

(2) According to the finding of the above (1), Invention 1 provides an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and

competes with reference antibody 1, and a pharmaceutical composition using the same. Invention 2 provides an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with reference antibody 2, and a pharmaceutical composition using the same. Further, it can be seen that a problem to be solved by each of the Inventions lies in the provision of such novel antibody and the preparation of a pharmaceutical composition using the same that can neutralize the binding of PCSK9 and LDLR and increase the amount of LDLR, thereby resulting in a reduction in the subject's serum cholesterol level and treating or preventing or reducing the risk of the diseases associated with increased cholesterol level such as hypercholesteremia.

Each of the specifications discloses that hybridomas have been prepared by use of immunized mice produced in accordance with the description of each of the specifications, and 2441 stable hybridomas producing an antibody that binds to PCSK9 have been established by screening, and it has been found that, of these, 39 antibodies in total were subjected to epitope binning, which resulted in 19 antibodies not competing with 31H4 but competing with 21B12 (BIN 1), out of which 15 antibodies were found to be neutralizing antibodies, and resulted in 10 antibodies not competing with21B12 but competing with 31H4 (BIN 3); of these, 7 antibodies were found to be neutralizing antibodies. Further, each of the specifications also discloses that 21B12 and 31H4 have excellent effects of blocking the binding of PCSK9 and EGFa domain of LDLR.

21B12 is included in reference antibody 1, and 31H4 is included in reference antibody 2. Thus, it can be seen that an antibody competing with 21B12 is an antibody competing with reference antibody 1 and an antibody competing with 31H4 is an antibody competing with reference antibody 2. Consequently, it is recognized that a person ordinarily skilled in the art who read each of the specifications would recognize that, in addition to the fact confirmed as a result of the above epitope binning assay that 15 specific antibodies of Invention 1 and 7 specific antibodies of Invention 2 are obtained, neutralizing antibodies competing with reference antibody 1 or 2 may be obtained through a similar epitope binning assay for the above remaining antibodies obtained from the above 2441 stable hybridomas and have an effect of causing the decrease of serum cholesterols in a subject.

Furthermore, each of the specifications describes the manufacture and selection of immunized mouse in accordance with a procedure and a schedule of immunization program in the description, the production of hybridomas using an immunized mouse, a screening, and an epitope binning assay for identifying an antibody that strongly

blocks the binding of PCSK9 and LDLR and competes with 21B12 or 31H4. It is recognized that based on these descriptions, a person ordinarily skilled in the art could recognize that neutralizing antibodies competing with reference antibody 1 or 2 might be obtained in addition to neutralizing antibodies competing with the reference antibody specifically described in each of the specifications, by repetitively implementing a series of procedures from the start.

As aforementioned, a person ordinarily skilled in the art can obtain an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with reference antibody 1 or 2 on the basis of the description of each of the specifications. Thus, novel antibodies of monoclonal antibodies of Inventions 1-1 and 2-1 are provided. Further, one can recognize the fact that a pharmaceutical composition of Inventions 1-2 and 2-2 using them may treat or prevent or reduce the risk of the diseases associated with increased cholesterol level such as hypercholesteremia. Therefore, it is recognized that each of the Inventions conforms to the support requirement.

(3) Appellant's allegation

Appellant alleges that each of the Inventions is an invention of an antibody specified only by a parameter requirement of "competing with reference antibody" and a problem to be solved by the invention (desired effect) "capable of neutralizing the binding" and a pharmaceutical composition using the same, but it cannot be said that a problem can be solved only by the competition, and thus the Inventions do not conform to the support requirement.

However, it cannot be said from the description of each of the specifications that "capable of neutralizing the binding" and "competing with reference antibody" are the relationship between a problem and a means for solving the problem, nor can it be said that the constituent feature to compete with reference antibody is a parameter requirement. Further, it is a matter of common general knowledge that amino acid sequence is identified in a process of identifying an antibody having specific binding properties. Therefore, it is not recognized as essential to specify the structure of the antibody (amino acid sequence) in advance for obtaining an antibody having specific binding properties (Exhibits Ko 34, 35).

As aforementioned, each of the Inventions provides an isolated monoclonal antibody that neutralizes the binding of PCSK9 and LDLR protein and competes with each of the reference antibodies, and has constituent features of being an isolated monoclonal antibody that "competes" with reference antibody and being capable of blocking ("neutralizing") the interaction (binding) between PCSK9 and LDLR. Thus,

the Appellant's allegation is not acceptable.

(4) Conformance to the support requirement of each of the corrected inventions

Note that Corrected Invention 1 further specifies reference antibody 1 of Invention 1 (constituent feature 1B) as reference antibody 1' (constituent feature 1B') by an amino acid sequence in a variable region. Note that Corrected Invention 2 further specifies reference antibody 2 of Invention 2 (constituent feature 2B) as reference antibody 2' (constituent feature 2B') by an amino acid sequence in a variable region, it is recognized that each of the corrected inventions conforms to the support requirement.

(5) Summary

As described above, it must be said that each of the Inventions and each of the corrected inventions conform to the support requirement.

4. Issue (2)B (Violation of Enablement Requirement)

(1) According to the finding of said 3(1), it can be seen from the description of each of the specifications that an antibody of Inventions 1-1 and 2-1 and a pharmaceutical composition of Inventions 1-2 and 2-2 may be produced and used, and thus it can be seen from the description of Detailed Description of the Invention of each of the specifications that a person ordinarily skilled in the art could definitely and sufficiently describe each of the Inventions to the extent that allows a person ordinarily skilled in the art to implement each of the Inventions.

Therefore, it is recognized that each of the Inventions conforms to the enablement requirement.

(2) Appellant's allegation

Appellant alleges that each of the Inventions does not identify the antibody structure, but defines only functionally, and includes an extremely broad range of antibodies, whereas it takes enormous time and effort as well as many trials and errors for a person ordinarily skilled in the art to obtain an antibody included in the whole range of each of the Inventions that does not specify the structure, and thus each of the Inventions fails to satisfy the enablement requirement.

However, the description of Detailed Description of the Invention of the specification is required to conform with the requirement that it should describe definitely and sufficiently to the extent that allows a person ordinarily skilled in the art to implement the invention, because in the absence of the description of the constitution of the invention, etc. in Detailed Description of the Invention of the specification to the extent that allows a person ordinarily skilled in the art to easily implement the invention, it can be traced to the non-disclosure of the invention, which

leads to lack of the prerequisite for granting to the inventor an exclusive right provisioned by the Patent Act.

Each of the Inventions is a technical idea for an isolated monoclonal antibody that competes with a reference antibody for binding with PCSK9 and is capable of neutralizing the binding of PCSK9 and LDLR protein. It cannot be said to be defined only functionally. Further, if the description of the Detailed Description of the Invention should have such a description that allows us to make an antibody which embodies a technical idea of an isolated monoclonal antibody that can neutralize the binding of PCSK9 and LDLR protein and competes with reference antibody 1 or 2 for binding with PCSK9, it must be said that a person ordinarily skilled in the art could implement the technical idea. It is not necessary to describe to the extent that every antibody having every amino acid sequence which can fall within a technical scope of the patent invention may be obtained.

Further, each of the Inventions is an invention of an antibody in which an amino acid to be recognized on an antigen is not specified. Thus, it must be said that it has nothing to do with the enablement requirement as to whether a specific antibody (EGFa mimic) that recognizes the most part of amino acids on PCSK9 that LDLR recognizes is described to work from the description of the Detailed Description of the Invention.

Further, as per the aforesaid (1), a person ordinarily skilled in the art can obtain a neutralizing antibody that competes with a reference antibody included in the scope of the claims of each of the Patents (Claim 1) in addition to the neutralizing antibodies that compete with a reference antibody described in each of the specifications in compliance with the description of each of the specifications. Thus, it cannot be said that it would take many trials and errors that go beyond the level that can be expected for a person ordinarily skilled in the art to obtain an antibody encompassed into the technical scope of each of the Inventions.

Therefore, the Appellant's allegation is not acceptable.

(3) Conformance to the enablement requirement of each of the corrected inventions

As per the aforesaid 3(4), it should be noted that Corrected Invention 1 further specifies reference antibody 1 of Invention 1 (constituent feature 1B) as reference antibody 1' (constituent feature 1B') by an amino acid sequence of a variable region. Note that Corrected Invention 2 further specifies reference antibody 2 of Invention 2 (constituent feature 2B) as reference antibody 2' (constituent feature 2B') by an amino acid sequence of a variable region. Therefore, a person ordinarily skilled in the art

can produce and use an antibody of Corrected Inventions 1-1 and 2-1 and a pharmaceutical composition of Corrected Inventions 1-2 and 2-2 from the description of each of the specifications. It is recognized that each of the Corrected Inventions conforms to the enablement requirement.

(4) Summary

As described above, it must be said that each of the Inventions and each of the corrected inventions conform to the enablement requirement.

5. Issues (2)C (Lack of Inventive step over Exhibit Otsu 1 Document)

(1) Described matters in Exhibit Otsu 1 document

The description from page 42, line 22 to page 46, line 23 of the judgment in prior instance is maintained. Thus, this is incorporated by reference.

(2) Finding of Exhibit Otsu 1 invention

A. According to the finding of the above (1), it is recognized that Exhibit Otsu 1 document discloses that [i] By an experiment adding a purified PCSK9 to a medium of cultured HepG2 cells, it was demonstrated that the purified PCSK9 reduced the number of cell-surface LDLRs of HepG2 cells in a dose- and time-dependent manner (Figures 2 and 3), [ii] We conclude from the experimental result of [i] that secreted PCSK9 associates with the LDLR and reduces hepatic LDLR protein levels, [iii] Genetic data from humans with loss-of-function mutations in PCSK9 combined with the studies in knockout mice that lack PCSK9 would be sufficient to inhibit the ability of an inhibitor of the protease activity of PCSK9 in cells to decrease LDLR level for the treatment of hypercholesterolemia; however, as suggested by data of this study, an additional method for neutralizing the activity of PCSK9 including the development of an antibody blocking the interaction (binding) between PCSK9 and LDLR and the development of an inhibitor blocking the activity in plasma may be sought as a treatment of hypercholesteremia.

Therefore, Exhibit Otsu 1 document describes "PCSK9 protein binding to LDLR" (hereinafter referred to as "Exhibit Otsu 1 Invention").

B. Appellant alleges that Exhibit Otsu 1 document discloses a PCSK9-LDLR binding neutralizing antibodies, which shares this point with each of the Inventions.

As in the aforesaid item (1)(cited Judgment in the prior instance, page 46, lines 19 to 23), however, Exhibit Otsu 1 document discloses an additional method for neutralizing the activity of PCSK9 including the development of an antibody blocking the interaction (binding) between PCSK9 and LDLR may be sought as a treatment of hypercholesteremia, whereas it fails to describe or suggest a specific antibody having such effect. Therefore, Exhibit Otsu 1 document fails to disclose an antibody itself

that blocks the interaction (binding) between PCSK9 and LDLR. Appellant's allegation is not acceptable.

(3) Comparison between each of the Inventions and Exhibit Otsu 1 invention

Comparing each of the Inventions with Exhibit Otsu 1 invention, they have in common that they are proteins, and have the following different features:

(Different Feature 1) Each of the Inventions is an "isolated monoclonal antibody", and an antibody "capable of neutralizing the binding of PCSK9 and LDLR protein" (constituent features 1A, 1C, 2A, 2C), whereas Exhibit Otsu 1 invention is not an isolated monoclonal antibody capable of neutralizing the binding of PCSK9 and LDLR protein.

(Different Feature 2A) Invention 1-1 is an antibody "competing" with reference antibody 1 "with respect to the competition with PCSK9" (constituent feature 1B'), whereas Exhibit Otsu 1 invention is silent about the competition with reference antibody 1 with respect to the competition with PCSK9.

(Different Feature 2B) Invention 2-1 is an antibody "competing" with reference antibody 2 "with respect to the competition with PCSK9" (constituent feature 2B'), whereas Exhibit Otsu 1 invention is silent about the competition with reference antibody 2 with respect to the competition with PCSK9.

(4) Well-known art as of the priority date

A. Exhibits Otsu 15 to 19 have the following descriptions:

(A) Exhibit Otsu 15 (Antibodies A LABORATORY MANUAL, 1988 (Showa 63-nen))

"For manipulating and adopting the reactivity against a certain antigen, there is only a little room left for researchers to be able to intervene. The types of such interventions are categorized into two categories. Specifically, to modify the antigen, or change the condition of infusion. ... The second kind of intervention includes the selection of animals, dose amount and forms of antigen, the use of immunoadjuvant, infusion path and times, and an interval between infusions." (page 92, lines 1 to 11)

"For the preparation of monoclonal antibody, both mouse and rat may be used. (...)" (page 94, lines 14 to 15)

(B) Exhibit Otsu 16 (Antibody Engineering Methods and Protocols, 2004 (Heisei 16-nen))

"A transgenic mouse in which a human immune globulin gene is introduced provides researchers with an opportunity to obtain complete human antibody by use of a well-established hybridoma technique. Several different strains of such mouse are available and accessible in a certain condition from various businesses. Brand

names of these mice are XenoMouse®, HuMAb mouse®, ..., and KM™ mouse." (page 191, main text, lines 1 to 6)

"3. Methods

3. 1 Preparation of all cells for immunization ...

3. 2 Immunization ...

3. 3 Preparation of lymphoid cell ...

3. 4 Isolation of B cell ...

3. 5 Cell Fusion ...

3. 6 Primary Screen of Antigen Binding...

3. 7 Secondary ELISA Screen...

3. 8 Hybridoma Cloning ..." (page 194, line 4 from the bottom to page 198, line 9)

"3.6 Primary Screen of Antigen Binding

1. An appropriate number of ELISA plates is ... into plate coating buffer (a buffer covering a plate surface) and in a case of using a plate (...) coated (a surface is covered) with a soluble antigen or streptoavidin, 100 to 300 ng/mL biotinylated antigen is coated (a surface is covered) at 50 uL/well." (page 197, lines 12 to 17)

"3.7 Secondary ELISA Screen

1. By use of a similar condition to Primary Screen (...), ELISA plates in double the number of cultivation plates are coated with 50 uL/well soluble or biotinylated antigen (a surface is covered)." (page 197, lines 33 to 36)

(C) Exhibit Otsu 17 (Phage Display of Peptides and Proteins A Laboratory Manual, 1996 (Heisei 8-nen))

"An antibody is a functional protein of cells that has been displayed on a surface of phage subsequent to the first demonstration (...) of peptide display (...). ... A region for the determination of binding specificity of antibody is a part called variable regions of heavy chain and light chain, and it is present at the N-terminal of each chain. The binding of heavy chain and light chain variable regions (respectively, VH and VL) results in the production of heterodimer molecule called Fv fragment and retains the binding specificity of the original antibody ....

The antibody may be expressed by Escherichia coli in the form of Fv fragment due to the other expression of VH and VL domains under the influence of signal peptide." (page 79, lines 1 to 12)

"In the other method, an antibody can express the form of FAb fragment in which various heavy chains bind to the whole light chain in addition to the first constant region." (page 80, lines 1 to 3)

"Preparation of the production of antibody gene and library ...

Preparation of PCR template ...
Protocol 2 Preparation of human peripheral blood lymphocyte ...
Protocol 3 Preparation of mouse or human antibody cDNA ... Construction of human V-gene repertoire
Protocol 4 Preparation of primary VH and VL PCR production ...
Protocol 11 Selection of phage antibody library by the selection (panning) in 'immune tube'...
Protocol 12 Selection of phage-antibody library by biotin selection ..." (page 81, line 34 to page 101, line 5 from the bottom)

"Screen and Expression of selected clone

Following selection (panning), individual colonies may be directly assayed for the ability to bind to a specific antigen. These may be screened by an immunoassay technology like ELISA as a phage particle or a soluble fragment." (page 105, lines 24 to 27)

(D) Exhibit Otsu 18 (REVIEW Selecting and screening recombinant antibody libraries, September 2005 (Heisei 17-nen))

"During the past decade several display methods and other library screening techniques have been developed for isolating monoclonal antibodies (mAbs) from large collections of recombinant antibody fragments. These technologies are now widely exploited to build human antibodies with high affinity and specificity." (page 1105, Abstract, lines 1 to 3)

"Phage Display

Antibody display on a surface of two kinds of bacteriophage fd and M13 is the most commonly used method for the display and selection of a large number of collections of antibodies and for the engineering of selected antibodies (...)." (page 1106, left column, line 10 to right column, line 2)

"FIG. 3

Method for ex vivo (in vitro) selection for binding. The selection from display library is implemented with several methods (or a combination thereof).

(...)

(b) Biotinylated antigen (Biotin (red) is captured via beads (gray) coated with Streptoavidin)" (page 1111)

(E) Exhibit Otsu 19 (REVIEWS Potent antibody therapeutics by design, May 2006 (Heisei 18-nen))

"Table 1 Monoclonal antibody approved for the therapeutic use in the United States" (page 344)

"The use of transgenic mouse for the manufacture of human antibody is relatively simple, and based on a widely used technique." (page 347, left column, lines 18 to 19)

"Human antibody from phage display library" (page 347, left column, line 9 from the bottom)

"After isolating from phage display library, several antibody fragments have sufficiently high binding affinity and biological effect for the indication of treatment." (page 347, the right column, lines 30 to 33)

"Affinity mature of the current antibody and the subsequent functional screening are widely used for promoting the effectiveness of antibodies, and are strategies that make a success at a high frequency." (page 350, right column, line 2 from the bottom to page 351, left column, line 2).

B. Comprehensively taking the description of the aforesaid A into account, it is recognized as a well-known technical matter that there were a method of utilizing hybridoma (Exhibits Otsu 15, 16) and a phage display method (Exhibits Otsu 17 to 19) as a method for producing monoclonal antibody having a specific binding to an antigen, and hybridoma method adopts the means of producing a number of hybridomas by use of cells sampled from a subject animal immunized by an antigen, and selecting an antibody having an ability to bind to an antigen by screening from antibodies produced by these hybridomas, and a phage display method adopts the means of preparing antibody genes and libraries on the basis of antibody gene obtained from human and animals and selecting an antibody having an ability to bind to an antigen as of the priority date.

(5) Determination about the different features

A. Different Feature 1

As aforementioned, Exhibit Otsu 1 document discloses that "an inhibitor of the protease activity of PCSK9 in cells would be sufficient to inhibit the ability to decrease LDLR level for the treatment of hypercholesterolemia; however, as is suggested by data of this study, an additional method for neutralizing the activity of PCSK9 including the development of an antibody blocking the interaction (binding) between PCSK9 and LDLR and the development of an inhibitor blocking the activity in plasma may be sought as a treatment of hypercholesteremia". This disclosure suggests the possibility of usefulness of antibody blocking the interaction (binding) between PCSK9 and LDLR and neutralizing the PCSK9 activity for the treatment of hypercholesteremia, and is thus recognized as a motivation for a person ordinarily skilled in the art who read Exhibit Otsu 1 to obtain a binding neutralizing antibody of

PCSK9 and LDLR.

Further, as per the aforesaid (4), it is recognized that a common method for the preparation of monoclonal antibody was well known by a hybridoma method or a phage display method as of the priority date.

Consequently, it is feasible to obtain any isolated monoclonal antibody capable of neutralizing the binding of PCSK9 and LDLR protein by applying well-known art to Exhibit Otsu 1 invention.

B. Different features 2A and 2B

However, Exhibit Otsu 1 document neither describes nor suggests competing with reference antibody 1 or 2 for binding with PCSK9, nor do they describe information that gives a clue for obtaining an antibody competing with reference antibody 1 or 2 from antibodies neutralizing the binding of PCSK9 and LDLR.

Further, as discussed in the aforesaid (4)B, it is recognized that every common means for obtaining monoclonal antibody of the well-known art comprises a step of producing a number of antibodies and a step of selecting an antibody by screening from these numerous antibodies, and a specific monoclonal antibody is obtained for the first time when an antibody is selected by screening. There is no evidence sufficient to find the fact that reference antibody 1 or 2 had been obtained before the priority date. It cannot be said that an antibody competing with reference antibody 1 or 2 could be selected by screening through competition assay.

Therefore, it cannot be recognized that a person ordinarily skilled in the art could have easily conceived of obtaining an antibody that competes with reference antibody 1 or 2 on the basis of Exhibit Otsu 1 invention and well-known art.

C. Based on the above fact, although a person ordinarily skilled in the art who read Exhibit Otsu 1 document could have easily conceived of obtaining any monoclonal antibody (Different Feature 1) capable of neutralizing the binding of PCSK9 and LDLR on the basis of Exhibit Otsu 1 invention and the above well-known art, it cannot be recognized that an antibody "competing" with reference antibody 1 or 2 was easily conceivable (different features 2A, B).

D. Appellant alleges that [i] each of the specifications describes that when a plurality of PCSK9-LDLR binding neutralizing antibodies are prepared without a barometer of whether or not to compete with reference antibody 1 or 2, almost all the antibodies compete with reference antibody 1 or 2; and [ii] According to the declaration statement by A, when PCSK9-LDLR binding neutralizing antibodies are obtained, of these, many antibodies competing with reference antibody 1 or 2 are contained, and this is why a person ordinarily skilled in the art could have easily

conceived of binding neutralizing antibodies competing with reference antibody 1 or 2 only by preparing several PCSK9-LDLR binding neutralizing antibodies on the basis of Exhibit Otsu 1 and well-known art as of the priority date.

However, each of the specifications describes in Table 37.1 that 2441 stable hybridomas had been established by confirmatory screening to produce an antibody binding to PCSK9 ([0329]), a part of which (39 antibodies in total) were subjected to epitope binning, and the results were summarized ([0489] to [0493]), and when this table is analyzed, it is difficult to derive a proportion of antibodies competing with a reference antibody in binding neutralizing antibody of PCSK9 and LDLR, and thus it cannot be said that most of PCSK9-LDLR binding neutralizing antibodies competed with reference antibody 1 or 2.

Further, the declaration statement by A stated that “most of anti-PCSK9 antibodies neutralizing the binding of PCSK9 and LDLR obviously compete with either of 21B12 or 31H4 in view of the binding site on PCSK9 surface of LDLR and the binding manner of these antibodies as depicted in Figure 27D (of each of the specifications)." (Exhibit Otsu 4). It only mentions that anti-PCSK9 antibodies neutralizing the binding of PCSK9 and LDLR compete with either of reference antibody 1 or 2, and it is not shown that most of PCSK9-LDLR binding neutralizing antibodies compete with reference antibody 1 or 2.

Therefore, as Appellant alleges, it cannot be said that Invention 1-1 or 2-1 was conceivable only by making PCSK9-LDLR binding neutralizing antibody.

In this regard, according to the description of Exhibit Otsu 15, it is recognized that in producing an antibody with an animal immunization method, antibodies with different reactivities against an antigen may be obtained by the difference in "an infusion condition" (for animals) including the selection of animals, a dosage amount and a dosage form of an antigen, the use of immunization adjuvant, the infusion route and times, and an interval between infusions (aforesaid (4)A(A)). It can be seen that this can apply similarly to animals for obtaining antibody gene used for the production of antibody in a phage display method. Incidentally, Exhibit Otsu 1 document does not at all describe the process for obtaining an antibody competing with reference antibody included in a specific condition of animal immunization. Thus, it cannot be said that it was easy to obtain reference antibody 1 or 2, which was an antibody having a specific amino acid sequence in a variable region even by applying general well-known art regarding the production of monoclonal antibody, nor can it be said that an antibody competing with reference antibody 1 or 2 could be obtained.

Therefore, the Appellant's allegation is not acceptable.

(6) Inventive step of each of the Corrected Inventions

A. Comparison between each of the Corrected Inventions and Exhibit Otsu 1 invention

Comparing each of the Corrected Inventions with Exhibit Otsu 1 invention, they have in common that they are proteins, and have the following different features in addition to Different Feature 1 between each of the Inventions and Exhibit Otsu 1 invention:

(Different feature 2A') Corrected Invention 1-1 is an antibody "competing" with reference antibody 1' "with respect to the competition with PCSK9" (constituent feature 1B'), whereas Exhibit Otsu 1 invention is silent about the competition with reference antibody 1' with respect to the competition with PCSK9.

(Different Feature 2B') Corrected Invention 2-1 is an antibody "competing" with reference antibody 2' "with respect to the competition with PCSK9" (constituent feature 2B'), whereas Exhibit Otsu 1 invention is silent about the competition with reference antibody 2' with respect to the competition with PCSK9.

B. Whether Different Features 2A' and 2B' were easily conceivable

Reference antibody 1' further specifies reference antibody 1 by an amino acid sequence in a variable region. Reference antibody 2' further specifies reference antibody 2 by an amino acid sequence in a variable region. Thus, for a similar reason for the fact that it is not easy to obtain an antibody competing with reference antibody 1 or 2, it must be said that it is also not easy to obtain an antibody competing with reference antibody 1' or 2'.

Therefore, it cannot be recognized that a person ordinarily skilled in the art could have easily conceived of obtaining an antibody that competes with reference antibody 1' or 2' on the basis of Exhibit Otsu 1 invention and well-known art.

(7) Summary

For the above reason, it cannot be said that each of the Inventions and each of the Corrected Inventions was easily conceivable by a person ordinarily skilled in the art on the basis of Exhibit Otsu 1 invention and well-known technique.

6. Issues (2) D (Lack of Inventive step over Exhibit Otsu 27 Document)

(1) Petition for dismissal of method of allegation or evidence Presented After Its Time Without Prejudice

Appellee alleges that the Appellant's allegation of lack of inventive step on the basis of the description of Exhibit Otsu 27 document and well-known art is a submission of petition of method of allegation or evidence presented after its time

without prejudice due to intention or serious fault that will delay the conclusion of litigation, and thus should be dismissed.

However, this suit had concluded oral proceeding on the date for oral argument when the above allegation was presented (Facts obvious to the court). It cannot be said that the above allegation will delay the conclusion of litigation. Therefore, the above Appellee's allegation is not acceptable.

(2) Described matters in Exhibit Otsu 27 document

Exhibit Otsu 27 document has the following descriptions:

A. When excreted PCSK9 is added to HEK293 cell, the decomposition of LDLR on cell surface was caused in a concentration-dependent and time-dependent manner. Accordingly, intracellular uptake of LDR was significantly decreased. When purified human PCSK9 was directly infused to C57B6 mice, LDLR protein level in liver is substantially decreased, thereby causing a result of elevating LDL cholesterol level in plasma. (page 1488, left column, lines 7 to 14)

B. PCSK9 interacts with LDLR extracellular domain.

... caused LDLR extracellular domain to be expressed as an excretion type, and the protein was purified (Figure 6A). After incubation together with recombinant PCSK9, LDLR was ... co-immuneprecipitated. A western blot analysis using PCSK9 antibody definitely shows the co-immuneprecipitation of PCSK9, which suggests the direct binding of PCSK9 to LDLR extracellular domain (Figure 6B). (page 1493, right column, line 1 to page 1494, left column, line 2)

C. In an additional experiment, we have demonstrated that the inhibition of the binding of PCSK9 to cell surface LDLR was sufficient to significantly weaken the function of PCSK9 through overexpression of LDLR extracellular domain, thereby being capable of characterizing the deterministic role of this direct interaction. Therefore, the binding of PCSK9 to LDLR extracellular domain is an essential step in the process of PCSK9 acting thereby to decrease LDLR protein level. (page 1497, left column, lines 8 to 15)

D. The drug inhibiting the specific function of PCSK9 will be developed as a method suitable for decreasing LDL and atherosclerosis. (page 1497, right column, lines 1 to 4)

(3) Finding of Exhibit Otsu 27 invention

According to the finding of the above (2), it is recognized that Exhibit Otsu 27 document demonstrates that the function of PCSK9 is significantly weakened by use of a protein that inhibits PCSK9 from binding to LDLR on cell surface by binding to PCSK9 outside the cell, and describes, as a result, proposing the use of a drug that

inhibits this specific function of PCSK9 as a pharmaceutical composition.

Therefore, it is recognized that Exhibit Otsu 27 document describes "LDLR extracellular protein binding to PCSK9" (hereinafter referred to as "Exhibit Otsu 27 invention".).

(4) Comparison between each of the Inventions and Exhibit Otsu 27 invention

Comparing Exhibit Otsu 27 invention with Inventions 1-1 and 2-1, they have in common that they are proteins binding to PCSK9, and have the following different features:

(Different Feature 1) Each of the Inventions is an "isolated monoclonal antibody", and a binding neutralizing antibody "capable of neutralizing the binding of PCSK9 and LDLR" (constituent features 1A, 1C, 2A, 2C), whereas Exhibit Otsu 27 invention is not an isolated monoclonal antibody capable of neutralizing the binding of PCSK9 and LDLR protein.

(Different Feature 2A) Invention 1-1 is an antibody "competing" with reference antibody 1 "with respect to the competition with PCSK9" (constituent feature 1B), whereas Exhibit Otsu 27 invention is silent about the competition with reference antibody 1 with respect to the competition with PCSK9.

(Different Feature 2B) Invention 2-1 is an antibody "competing" with reference antibody 2 "with respect to the competition with PCSK9" (constituent feature 2B), whereas Exhibit Otsu 27 invention is silent about the competition with reference antibody 2 with respect to the competition with PCSK9.

(5) Determination about the different features

A. Exhibit Otsu 27 document does not describe an antibody neutralizing the binding of PCSK9 and LDLR, nor does it suppose replacing a protein binding to an LDLR extracellular domain with an antibody, and thus it must be said that there is no motivation to replace LDLR extracellular domain protein binding to PCSK9 of Exhibit Otsu 27 invention with PCSK9-LDLR binding neutralizing antibody.

Therefore, it cannot be recognized that a person ordinarily skilled in the art could easily conceive of the constitution according to the above Different Feature 1.

Therefore, it is obvious that Inventions 1-1 and 2-1 were not easily conceivable by a person ordinarily skilled in the art on the basis of Exhibit Otsu 27 invention, nor were Inventions 1-2 and 2-2, which relate to a pharmaceutical composition including these antibodies, easily conceivable by a person ordinarily skilled in the art on the basis of Exhibit Otsu 27 invention.

B. Appellant alleges that it was a well-known matter as of the priority date that a representative example of inhibitor capable of inhibiting the binding of one protein

and another protein outside the cell (in blood) may include an antibody (usually monoclonal antibody particularly for pharmaceutical use), and Exhibit Otsu 1 document and Exhibit Otsu 28 document explicitly propose an antibody as a PCSK9-LDLR inhibitor, and thus there was a motivation for replacement.

However, as aforementioned, Exhibit Otsu 1 document discloses that an additional method of neutralizing the activity of PCSK9, involving the development of antibody blocking the interaction of PCSK9 and LDLR or an inhibitor blocking the activity in plasma, may be sought for the treatment of hypercholesteremia. Further, Exhibit Otsu 28 document describes "an antibody or small molecule binding to PCSK9 in plasma to inhibit the binding of PCSK9 and LDLR may be an effective inhibitor for the function of PCSK9"; however, it does not disclose the replacement itself of an inhibitor with an antibody. Therefore, it cannot be said from these descriptions that it was a well-known art to replace an inhibitor with an antibody. Thus, the Appellant's allegation is not acceptable.

C. Even if the replacement of an inhibitor with an antibody was a well-known art and it was possible to obtain PCSK9-LDLR binding neutralizing antibodies (Different Feature 1) by applying such well-known art or well-known art for the method of producing common monoclonal antibody as found in said 5(4), Exhibit Otsu 27 document neither describes nor suggests competing with reference antibody 1 or 2 for binding with PCSK9, nor does it describe information that gives a clue for obtaining an antibody competing with reference antibody 1 or 2 from antibodies neutralizing the binding of PCSK9 and LDLR. Further, there is no evidence sufficient to find the fact that reference antibody 1 or 2 had been obtained before the priority date. It cannot be said that an antibody competing with reference antibody 1 or 2 could be selected by screening through competition assay by applying the means for obtaining a common monoclonal antibody in well-known art, as per the aforesaid 5(5)B.

Therefore, it cannot be said that a person ordinarily skilled in the art could have easily conceived of obtaining reference antibody 1 or 2, nor can it be recognized that the constitution according to Different Feature 2 was easily conceivable.

(6) Inventive step of each of the Corrected Inventions

A. Comparison between each of the Corrected Inventions and Exhibit Otsu 27 invention

Comparing each of the Corrected Inventions with Exhibit Otsu 27 invention, they have in common that they are proteins binding to PCSK9, and have the following different features in addition to Different Feature 1 between each of the Inventions

and Exhibit Otsu 27 invention:

(Different Feature 2A') Corrected Invention 1-1 is an antibody "competing" with reference antibody 1' "with respect to the competition with PCSK9" (constituent feature 1B'), whereas Exhibit Otsu 27 invention is silent about the competition with reference antibody 1' with respect to the competition with PCSK9.

(Different Feature 2B') Corrected Invention 2-1 is an antibody "competing" with reference antibody 2' "with respect to the competition with PCSK9" (constituent feature 2B'), whereas Exhibit Otsu 27 invention is silent about the competition with reference antibody 2' with respect to the competition with PCSK9.

B. Whether Different Features 2A' and 2B' were easily conceivable

Reference antibody 1' further specifies reference antibody 1 by an amino acid sequence in a variable region. Reference antibody 2' further specifies reference antibody 2 by an amino acid sequence in a variable region. Thus, for a similar reason for the fact that it is not easy to obtain an antibody competing with reference antibody 1 or 2, it must be said that it is also not easy to obtain an antibody competing with reference antibody 1' or 2'.

Therefore, it cannot be recognized that a person ordinarily skilled in the art could have easily conceived of obtaining an antibody that competes with reference antibody 1' or 2' on the basis of Exhibit Otsu 27 invention and well-known art.

(7) Summary

For the above reason, it cannot be said that each of the Inventions and each of the Corrected Inventions were easily conceivable by a person ordinarily skilled in the art on the basis of Exhibit Otsu 27 invention and well-known technique.

7. Issues (3) (Propriety of injunctive relief)

(1) According to the aforesaid findings 1 to 6, it is not recognized that Defendant's monoclonal antibody falls within a technical scope of Inventions 1-1 and 2-1, Defendant's product falls within a technical scope of Inventions 1-2 and 2-2, and further each of Patent 1 and 2 should be invalidated by a trial for patent invalidation.

As aforementioned, there is no dispute between parties concerned that Appellant imports, transfers, and offers to transfer Defendant's products (cited Judgment in prior instance, page 7, line 2). These acts correspond to infringing acts of patent rights 1 and 2.

(2) Necessity of injunction of production of Defendant's products and production, import, transfer, and offer to transfer Defendant's monoclonal antibody

Appellant alleges that Appellant does not produce Defendant's products, nor does it produce, import, transfer, and offer to transfer its raw material of Defendant's

monoclonal antibody.

According to the entire import of the oral argument, however, it is recognized that Appellant can import Defendant's monoclonal antibody, which is an active pharmaceutical ingredient of Defendant's product, from the parent company Sanofi, etc. of France, and Defendant's monoclonal antibody may be easily produced by subjecting a cell strain for the production of Defendant's monoclonal antibody to clonal culture. Thus, it cannot be ruled out that Appellant might possibly produce Defendant's product or transfer Defendant's monoclonal antibody following the import or production of Defendant's monoclonal antibody, and thus it must be said that Appellant is likely to produce Defendant's product or conduct each of an act of production, import, transfer, and offer to transfer of Defendant's monoclonal antibody.

Consequently, these acts possibly infringe Patent Rights 1 and 2. Thus, the necessity of the injunction is recognized.

(3) Abuse of rights

Appellant submits the expert opinion prepared by B (Exhibit Otsu 33), alleging that Appellee's claim for injunction corresponds to the abuse of rights and thus is not permitted since the injunction of the production and transfer, etc. of Defendant's product and Defendant's monoclonal antibody causes patients currently administered or to be administered Defendant's product to have severe health risk or anxiety for future therapy.

Exhibit Otsu 33 points out the problem of decreasing options for patients and expecting the bafflement of patients who use Defendant's product caused by the injunction of transfer, etc. of Defendant's product; however, it does not go so far as to point out the occurrence of concrete health risk for patients by use of products produced and sold by Appellee in place of Defendant's product. Thus, it cannot be said that specific facts have been demonstrated that the injunction of the use of Defendant's product is contrary to the public interest.

Further, in the field of pharmaceutical products, there might be the case where a right to seek injunction should be limited from a viewpoint of public interests; however, it cannot be concluded that an injunction of the production, transfer, etc. of infringing products should not be permitted, without establishing concrete facts, for a simple reason that it is desirable for patients to have a selectable option. Therefore, the Appellant's allegation is not acceptable.

(4) Summary

As seen above, all the Appellee's claims against Appellant for an injunction of the production, transfer, import, and offer to transfer of Defendant's product and

Defendant's monoclonal antibody and a disposal of Defendant's product under Article 100, paragraph (1) and (2) of the Patent Act on the basis of each of the patent rights have a point.

8. Conclusion

As described above, the judgment in the prior instance that accepted a claim for an injunction of the Appellee's production, transfer, import, and offer to transfer of Defendant's product and Defendant's monoclonal antibody and a claim for disposal of Defendant's product and dismissed the remaining claim is reasonable, and thus the appeal shall be dismissed, and a judgment shall be made as described in the main text.

Intellectual Property High Court, First Division
Presiding Judge TAKABE Makiko
Judge KOBAYASHI Yasuhiko
Judge SEKINE Sumiko

Attachment

Table 2

Typical heavy chain and light chain variable regions

Antibody	Light chain /Heavy chain variable regions SEQ NO.
30A4	5/74
3C4	7/85
23B5	9/71
25G4	10/72
31H4	12/67
27B2	13/87
25A7	15/58
27H5	16/52
26H5	17/51
31D1	18/53
20D10	19/48
27E7	20/54
30B9	21/55
19H9	22/56
26E10	23/49
21B12	23/49
17C2	24/57
23G1	26/50
13H1	28/91
9C9	30/64
9H6	31/62
31A4	32/89
1A12	33/65
16F12	35/79
22E2	36/80
27A6	37/76
28B12	38/77
28D6	39/78
31G11	40/83
13B5	42/69
31B12	44/81
3B6	46/60

Table 3

Mouse strain	XMG2/k1	XMG4/k1
Number of animals	10	10
Immunogen	PCSK9-V5/His	PCSK9-V5/His
First enhanced	Intraperitoneal injection	Intraperitoneal injection

immunization	10 μg for each	10 μg for each
	Titermax Gold	Titermax Gold
Second enhanced immunization	Tail injection 5 μg for each	Tail injection 5 μg for each
	Alum/CpG ODN	Alum/CpG ODN
Third enhanced immunization	Intraperitoneal injection 5 μg for each	Intraperitoneal injection 5 μg for each
	Titermax Gold	Titermax Gold
Fourth enhanced immunization	Tail injection 5 μg for each	Tail injection 5 μg for each
	Alum/CpG ODN	Alum/CpG ODN
Fifth enhanced immunization	Intraperitoneal injection 5 μg for each	Intraperitoneal injection 5 μg for each
	Titermax Gold	Titermax Gold
Sixth enhanced immunization	Tail injection 5 μg for each	Tail injection 5 μg for each
	Alum/CpG ODN	Alum/CpG ODN
Seventh enhanced immunization	Intraperitoneal injection 5 μg for each	Intraperitoneal injection 5 μg for each
	Titermax Gold	Titermax Gold
Eighth enhanced immunization	Tail injection 5 μg for each	Tail injection 5 μg for each
	Alum/CpG ODN	Alum/CpG ODN
Blood sampling		
Ninth enhanced immunization	Intraperitoneal injection 5 μg for each	Intraperitoneal injection 5 μg for each
	Titermax Gold	Titermax Gold
Tenth enhanced immunization	Tail injection 5 μg for each	Tail injection 5 μg for each
	Alum/CpG ODN	Alum/CpG ODN
Eleventh enhanced immunization	BIP 5 μg for each	BIP 5 μg for each
	PBS	PBS
Sampling		

Table 8.3

Clone	BIN
21B12.2	1
31H4	3
20D10	1
25A7.1	2
25A7.3	1
23G1	1
26H5	1
31D1	1
16F12	3
28D6	3
27A6	3
31G11	3
27B2	ND
28B12	3
22E2	3
1A12.2	1
3B6	1
3C4	4
9C9	1
9H6	1
13B5	6
13H1	7
17C2	1
19H9.2	1
23B5	1
25G4	1
26E10	1
27E7	1
27H5	1
30A4	1
30B9	1

Clone	BIN
31A4	5
31B12	5

Table 37.1

BIN 1	BIN 2	BIN 3	BIN 4	BIN 5
01A12.2	27B2.1	16F12.1	11G1.5	30A4.1
03B6.1	27B2.5	22E2.1	03C4.1	13B5.1
09C9.1	12H11.1	27A6.1		13H1.1
17C2.1		28B12.1		31A4.1
21B12.2		28D6.1		31B12.1
23G1.1		31G11.1		
25G4.1		31H4.1		
26E10.1		08A1.2		
11H4.1		08A3.1		
11H8.1		11F1.1		
19H9.2				
26H5.1				
27E7.1				
27H5.1				
30B9.1				
02B5.1				
23B5.1				
27B2.6				
09H6.1				