Trial decision

Invalidation No. 2016-800004

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The case of trial regarding the invalidation of Japanese Patent No. 5705288, titled "ANTIGEN BINDING PROTEINS TO PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)" between the parties above has resulted in the following trial decision:

Conclusion

The scope of claims of Patent No. 5705288 shall be corrected in accordance with Claims [1 to 4, 9] and [5 to 8] after the correction as in the corrected scope of claims attached to the written correction request.

The claim for trial concerning the inventions according to Claims 1 and 9 of Patent No. 5705288 should be dismissed.

A non-compliant claim for trial with respect to an invention according to Claims 2 to 8 of Patent No. 5705288 should be dismissed by a decision.

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

Reason

No. 1 History of the procedures

The patent according to Patent No. 5705288 is derived from Japanese Patent Application No. 2013-195240 filed on September 20, 2013, which is a divisional application of Japanese Patent Application No. 2010-522084 with an international filing date of August 22, 2008 (claiming priority under Paris convention on August 23, 2007 (US), December 21, 2007 (US), January 9, 2008 (US), August 4, 2008 (US)), and registered on March 6, 2015.

Demandant made a request for a patent invalidation trial with regard to the inventions recited in Claims 1 to 9 of the Patent on January 18, 2016. History of procedure in the Invalidation Trial of the case is as follows.

January 18, 2016 Written demand for Trial
June 2, 2016 Written reply, Written correction request
September 5, 2016 Written refutation (1), Written refutation (2)
December 21, 2016 Notification of matters to be examined (the date is drafting date)
February 3, 2017 Oral proceedings statement brief (Demandant)
February 3, 2017 Oral proceedings statement brief ([Demandee])
February 21, 2017 Written Statement (Demandant)
February 24, 2017 Oral proceeding
March 9, 2017 Advance notice of a trial decision
May 8, 2017 Written correction request
July 6, 2017 Written Statement (Demandant)

No. 2 Request for correction

1 Object of correction request and the content of correction

The correction requested by Demandee with the written correction request on May 8, 2017 requests for the correction of the scope of claims of the Patent as per the corrected scope of the claims attached to the written correction request.

The content of the correction includes the correction according to a unit of claims consisting of Claims 1 to 4 and 9, and the correction according to a unit of claims consisting of Claims 5 to 8 as set forth below (the underlined parts are the corrected parts).

(1) Correction A (Correction according to Claim 1)

"[Claim 1] An isolated monoclonal antibody capable of neutralizing the binding of PCSK9 and LDLR protein, competing with the antibody comprising: a heavy chain comprising CDR1, 2 and 3 respectively consisting of the amino acid sequences of SEQ ID NO. 368, 175 and 180; and a light chain CDR1, 2 and 3 respectively consisting of the amino acid sequences of SEQ ID NO. 158, 162 and 395 in regard to the binding with PCSK9."

is to be corrected as follows:

"[Claim 1] An isolated monoclonal antibody capable of neutralizing the binding of PCSK9 and LDLR protein, competing with <u>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</u> in regard to the binding with PCSK9."

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(2) Correction B (Correction according to Claim 2)
Claim 2 is canceled.

(3) Correction C (Correction according to Claim 3)
Claim 3 is canceled.

(4) Correction D (Correction according to Claim 4)
Claim 4 is canceled.

(5) Correction E (Correction according to Claim 5)
Claim 5 is canceled.

(6) Correction F (Correction according to Claim 6)
Claim 6 is canceled.

(7) Correction G (Correction according to Claim 7)
Claim 7 is canceled.

(8) Correction H (Correction according to Claim 8)
Claim 8 is canceled.

(9) Correction I (Correction according to Claim 9)
"[Claim 9] A pharmaceutical composition comprising an isolated monoclonal antibody of any one of Claims 1 to 8."
is to be corrected as follows:
"[Claim 9] A pharmaceutical composition comprising the isolated monoclonal antibody of Claim 1."

2 Judgement of suitability of correction
(1) Regarding a unit of claims
Claims 2 to 4 and 9 before the correction depend from Claim 1. These claims are corrected in accordance with Claim 1 to be corrected by Correction A. Thus Claims 1 to 4 and 9 are within a unit of claims as provided in Article 134-2(3) of the Patent Act.
Further, Claims 6 to 8 before the correction depend from Claim 5. These claims are corrected in accordance with Claim 5 to be corrected by Correction E. Thus Claims 5 to 8 are within a unit of claims as provided in Article 134-2(3) of the Patent Act.
Therefore, the Correction A to D and I with regard to Claims 1 to 4 and 9 and the Correction E to H with regard to Claims 5 to 8 are made within a unit of claims, and conform to the provision of Article 134-2(3) of the Patent Act.

(2) Correction A
It is obvious from Figure 13C and Figure 3JJ attached to the application that SEQ ID NOS. 368, 175 and 180 of Claim 1 before the correction are amino acid sequences of CDR1, CDR2 and CDR3 of heavy chain of 21B12 antibody, and SEQ ID NO. 49 of Claim 1 after the correction is amino acid sequence of heavy chain variable

region of 21B12 antibody, and the amino acid sequence of SEQ ID NO. 49 comprises amino acid sequences of SEQ ID NOS. 368, 175 and 180. Further, it is obvious from Figure 13A and Figure 3JJ attached to the application that SEQ ID NOS. 158, 162 and 395 of Claim 1 before the correction are amino acid sequences of CDR1, CDR2 and CDR3 of light chain of 21B12 antibody, and SEQ ID NO. 23 of Claim 1 after the correction is amino acid sequence of light chain variable region of 21B12 antibody, and the amino acid sequence of SEQ ID NO. 23 comprises amino acid sequences of SEQ ID NOS. 158, 162 and 395.

As in the foregoing, Correction A corrects an antibody specified by three CDRs of heavy chain and three CDRs of light chain with an antibody specified by the whole heavy chain variable region and the whole light chain variable region. Therefore, the Correction A is intended to "restrict the scope of claims" as specified in the item (i) of the proviso to Article 134-2(1) where of the Patent Act.

Further, as aforementioned, these corrections are made within a scope of matters described in the drawings, and it does not substantially enlarge or alter the scope of claims, and thus conforms to the provisions of Articles 126(5) and 126(6) as applied mutatis mutandis to Article 134-2(9) of the Patent Act.

(3) Regarding corrections B to H

The corrections B to H are to cancel Claims 2 to 8. Therefore, the corrections are aiming at "the restriction of the scope of claims" provisioned in item (i) of the proviso to Article 134-2(1) of the Patent Act.

Further, these corrections are made within a scope of matters described in the drawings, and obviously it does not substantially enlarge or alter the scope of claims, and thus conforms to the provisions of Articles 126(5) and 126(6) as applied mutatis mutandis to Article 134-2(9) of the Patent Act.

(4) Regarding correction I

The Correction I corrects the dependency of "any one of Claims 1 to 8" of Claim 9 before the correction with the dependency only on Claim 1, which corresponds to "a correction for the purpose of dissolving the reference of a claim to the other claims and making the claim independent from the other claims", as provisioned in the item (iv) of the proviso to Article 134-2(1) of the Patent Act.

Further, this correction is made within a scope of matters described in the drawings, and it does not substantially expand or change the scope of claims, and thus conforms to the provisions of Articles 126(5) and 126(6) as applied mutatis mutandis to Article 134-2(9) of the Patent Act.

3 Conclusion as to the request for correction

As described above, the correction is aiming at the matter listed in the items (i) and (iv) of the proviso to Article 134-2(1) of the Patent Act, and complies with the provision of Articles 126(5) to (6) of the Patent Act as applied mutatis mutandis pursuant to Article 134-2(9) of the Patent Act. Therefore, the correction should be approved for a unit of claims.

No. 3 Corrected invention of the case

The inventions according to Claims 1 to 9 of the patent should be specified as in

the following by the matters recited in Claims 1 to 9 of the scope of claims of Correction of the case:

"[Claim 1] An isolated monoclonal antibody capable of neutralizing the binding of PCSK9 and LDLR protein, 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 in regard to the binding with PCSK9.

[Claim 9] A pharmaceutical composition comprising an isolated monoclonal antibody of Claim 1."
(Hereinafter referred to as "Corrected Invention 1" and "Corrected Invention 9", respectively.)

No. 4 Allegations of the parties and Means of proof
1 Demandant's allegation and Means of proof

Demandant demands a decision to the effect that "Patents regarding the inventions according to Claims 1 to 9 of Patent No. 5705288 shall be invalidated. The costs in connection with the trial shall be borne by Demandee." on the grounds of the following reasons for invalidation 1 to 4 and submits Evidence A No. 1 to 12 as means of proof.

(1) Reasons for invalidation 1 (violation of requirements for support)

Corrected Inventions 1 and 9 encompass various structures of antibodies defined only by their function without structural limitation. It cannot be said that even a person skilled in the art could expand or generalize the matters described in the Detailed Description of the Invention to the whole range of antibodies.

Therefore, this case does not conform to the requirements under Article 36(6)(i) of the Patent Act.

(2) Reasons for invalidation 2 (noncompliance of enablement requirement)

It cannot be said that the Detailed Description of the Invention fails to disclose definitely and sufficiently to the extent that allows a person skilled in the art to make antibodies with various structures encompassed into Corrected Inventions 1 and 9.

Therefore, this case does not conform to the requirements under Article 36(4)(i) of the Patent Act.

(3) Reasons for invalidation 3 (violation of requirements for clarity)

According to the Detailed Description of the Invention, "an epitope of an antibody comprising: a heavy chain comprising CDR1, 2 and 3 respectively consisting of the amino acid sequences of SEQ ID NO. 368, 175 and 180; and a light chain CDR1, 2 and 3 respectively consisting of the amino acid sequences of SEQ ID NO. 158, 162 and 395" of Claim 5 of the Patent is a steric structural epitope, and it is not definitely disclosed as to what amino acid constitute epitope. Therefore, the scope of "an isolated monoclonal antibody that recognizes completely or partially same epitope" as the antibody is indefinite.

Therefore, this case does not conform to the requirements under Article 36(6)(ii) of the Patent Act.

(4) Reasons for invalidation 4 (Lack of inventive step)

Evidence A No. 1 provides a motivation to obtain an antibody neutralizing the interaction between PCSK9 and LDLR for the treatment of hypercholesteremia and test its utility. Thus a person skilled in the art could have easily conceived of Corrected Inventions 1 and 9 by the combination with a well-known art to prepare a monoclonal antibody.

Therefore Corrected Inventions 1 and 9 are not patentable under the provision of Article 29(2) of the Patent Act.

[Means of proof]
Evidence A No. 1: J. Clin. Invest., vol. 116(11), pp.2995-3005 (2006)
Evidence A No. 2: Published appeal and trial decision (Appeal No. 2010-7407, decision on October 9, 2012)
Evidence A No. 3: Published appeal and trial decision (Appeal No. 2013-12494, decision on January 19, 2015)
Evidence A No. 4: Published appeal and trial decision (Appeal No. 2010-4484, decision on September 3, 2012)
Evidence A No. 5: The written opinion dated September 20, 2013 of the original application (Japanese Patent Application No. 2010-522084) of the application
Evidence A No. 6: Published appeal and trial decision (Appeal No. 2005-21528, decision on November 7, 2006)
Evidence A No. 7: CAFC ruling (AbbVie Deutschland GmbH v. Janssen Biotech, Inc. No. 2013-1338,-1346 (Fed.Cir.7/1/2014))
Evidence A No. 8: Examination Handbook of Patent and Utility, Appendix A, "Cases regarding description requirement" [Case 2].
Evidence A No. 9: IP High Court Ruling on November 11, 2005 (Heisei 17-nen (Gyo-Ke) No. 10042).
Evidence A No. 10: IP High Court Ruling on February 20, 2013 (Heisei 24-nen (Gyo-Ke) No. 10151).
Evidence A No. 11: TRENDS in Biochem. Sci., vol. 32(2), pp.71-77 (2007)
Evidence A No. 12: IP High Court Ruling on May 10, 2010 (Heisei 21-nen (Gyo-Ke) No. 10170)

2 Demandee's allegation and Means of proof

Demandee demands that none of the reasons for invalidation 1 to 4 as Demandant alleges has a point, and submits Evidence B No. 1 to 21 as means of proof:

[Means of proof]
Evidence B No. 1: Proc. Natl. Acad. Sci. USA., vol. 100(3), pp.928-933 (2003)
Evidence B No. 2: Arterioscler. Thromb. Vasc. Biol., vol. 24, pp.1448-1453 (2004)
Evidence B No. 3: Proc. Natl. Acad. Sci. USA., vol. 102(6), pp.2069-2074 (2005)
Evidence B No. 4: TRENDS in Biochem.Sci., vol. 32(2), pp.71-77 (2007)
Evidence B No. 5: J. Lipid Res., vol. 48, pp.763-767 (2007)
Evidence B No. 6: A website (Firstwordpharma)
Evidence B No. 7: A press release (Santaris Pharma A/S)
Evidence B No. 8: United States Patent No. 7,605,251 (Cover letter)

Evidence B No. 9: Handbook of Patent and Utility Model Examination, Appendix B, Chapter 2, pages 1 to 14
Evidence B No. 10: Handbook of Patent and Utility Model Examination, Appendix B, Chapter 2, pages 72 to 73
Evidence B No. 11: Examination Guidelines for Patent and Utility Model, Part II, Chapter 1, Enablement requirement, pages 1 to 5
Evidence B No. 12: "Epitope", Seikagaku Jiten, Third Edition
Evidence B No. 13: Handbook of Patent and Utility Model Examination, Appendix A1, pages 1 to 11
Evidence B No. 14: IP High Court Ruling on August 31, 2010 (Heisei 21-nen (Gyo-Ke) No. 10434).
Evidence B No. 15: J. Clin. Invest., vol. 116(11), pp.2995-3005 (2006)
Evidence B No. 16: A supplementary document of Evidence A No. 1 published together with Evidence A No. 1
Evidence B No. 17: Declaration on January 25, 2017 by Kelly Berry
Evidence B No. 18: Declaration on January 25, 2017 by Wei Wong
Evidence B No. 19: Declaration on January 30, 2017 by Joyce, Chee Ye Chan
Evidence B No. 20: Declaration on January 30, 2017 by Chadwick King
Evidence B No. 21: J. Biol. Chem., vol. 285(17), pp.12882-12891 (2010)

No. 5 Judgment by the body

The body determines that none of the reasons for invalidation 1 to 4 has a point. The reason is set forth below.

1 Regarding Reasons for invalidation 1 (violation of requirements for support)
(1) Details of Demandant's allegation

The reason for invalidation 1 as Demandant alleges is set forth below:

A "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 in regard to the binding with PCSK9" of Corrected Invention 1 is only a functional description, not providing a structural limitation. Thus Corrected Invention 1 encompasses antibodies with various structures.

In contrast, it is only the reference antibody of 21B12 antibody that is experimentally demonstrated by the Detailed Description of the Invention to be both included into Corrected Invention 1, i.e. "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 in regard to the binding with PCSK9" and "capable of neutralizing the binding of PCSK9 and LDLR protein".

21B12 antibody cannot be expanded or generalized to the whole scope of Corrected Invention 1 including antibodies with various structures. The same can also apply to Corrected Invention 9.

B Example 37 of the Detailed Description of the Invention (Table 37.1) describes 19 kinds for BIN 1 (antibody not competing with 31H4 antibody but competing with 21B12 antibody) and 3 kinds for BIN 2 (antibody competing with both 21B12 antibody and 31H4 antibody) as an antibody competing with 21B12 antibody,

the ability of these antibodies to neutralize describes "non-neutralization", "weak neutralization" or "strong neutralization" in the paragraph [0138].

The paragraph describes that "neutralization" encompasses two concepts of "neutralization by the prevention of the binding of PCSK9 and LDLR" (corresponding to "capable of neutralizing the binding of PCSK9 and LDLR" of Corrected Invention 1. Hereinafter referred to as "neutralization of embodiment 1".) and "neutralization by the prevention of PCSK9-mediated decomposition of LDLR without preventing the binding of PCSK9 and LDLR" (hereinafter referred to as "neutralization of embodiment 2".) It is indefinite as to which concept of the neutralizing ability the antibodies of BIN 1 and BIN 2 have. Thus it cannot be said that these antibodies are encompassed into Corrected Invention 1.

Even if the neutralizing ability of the total 22 kinds of antibodies of BIN 1 and BIN 2 should be the neutralization of embodiment 1, these antibodies are encompassed into Corrected Invention 1. Even so, however, comparing CDR sequences of heavy chain and light chain of each antibody, it provides at most three groups of antibodies such as group 1 having a high similarity to 21B12 antibody, group 2 having a high similarity to 1A12 antibody, and group 3 having a high similarity to 23B5 antibody.

There only three groups of antibodies cannot be expanded or generalized to the whole scope of Corrected Invention 1 including antibodies with various structures. The same can also apply to Corrected Invention 9.

(2) Judgment by the body

A Matters described in the Detailed Description of the Invention

The Detailed Description of the Invention describes the following matters:

(A) Suppressing the interaction of PCSK9 and LDLR results in the increased amount of LDLR that can bind to LDL, thereby decreasing LDL amount in serum, and reducing cholesterols in serum. (Paragraph [0066])

(B) The 21B12 antibody is an anti-PCSK9 antibody 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. (Paragraph [0002], Table 2)

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

(D) The term "competing" means the competition between antibodies determined by various assays (known documents about assay method are cited.) 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 or overlapping with the reference antibody, and an antibody binding to an adjacent epitope sufficiently closed to interfere sterically the binding of the reference antibody to the epitope. These antibodies are expected to show functional properties similar to the reference antibody. (Paragraphs [0140] and [0269])

(E) 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 (Paragraph [0142])

(F) For 3000 kinds of anti-human PCSK9 monoclonal antibodies obtained by immunizing mice having human immuno globulin gene with human PCSK9, a screening by the binding ability to wild-type PCSK9, a screening by the cross reactivity to mouse PCSK9, a screening by the binding ability to PCSK9D374Y mutant and a screening by the binding blocking ability of PCSK9D374 mutant and LDLR (the mutant has a higher binding affinity to LDLR compared to wild-type) were implemented to identify 85 kinds of antibodies. (Examples 1 to 3)

(G) Specific examples of typical antibody (Table 2)

表　2
典型的な重鎖及び軽鎖可変領域

抗体	軽／重 配列番号
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

表２　Table 2
典型的な重鎖及び軽鎖可変領域　Typical heavy chain and light chain variable region

抗体　Antibody
軽／重配列番号　Light/heavy sequence number

(H) From antibodies of Table 2, 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. (Paragraph [0138])

(I) Result of Epitope Binning (Example 10, Table 8.3)

表　8.3

クローン	ビン
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

クローン	ビン
31A4	5
31B12	5

表８．３　Table 8.3
クローン　Clone

ビン　BIN

BINs 1 (competes with 21B12 antibody) and 3 (competes with 31H4 antibody) are exclusive of each other; BIN 2 competes with BINs 1 and 3; and BIN 4 does not compete with BINs 1 and 3. (Paragraph [0494])

(J) 21B12 antibody blocks the binding of PCSK9 and LDLR. (Example 11)

(K) 21B12 antibody blocks the LDL intake into cells. (Example 12)

(L) The crystal structure analysis of 21B12 antibody/PCSK9 composite shows that specific core PCSK9 amino acid residue (residue number is SEQ ID NO.3.) present within 5 angstrom from 21B12 antibody at an interactive interface of them is S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, and F379. (Example 30)

(M) A Result of Epitope Binning (Example 37, Table 37.1)

表　37.1.

ビン１	ビン２	ビン３	ビン４	ビン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				

表３７．１　Table 37.1
ビン　BIN

(N) According to epitope binning using arginine/glutamic acid scanning, the epitope of 21B12 antibody is a steric structural epitope. Amino acid residue "hit" of PCSK9 that varies the antibody binding ability (EC50 shift, Bmax shift) when substituted with arginine or glutamic acid is believed to be a part of epitope. (Examples 39, Table 39. 5)

表 39.5

EC50シフトのヒット					Bmaxシフトのヒット				
21B12	31H4	31A4	12H11	3C4	21B12	31H4	31A4	12H11	3C4
R207E	R185E	R439E	T132R	E582R	D162R			S123R	R519E
D208R*		E513R	S351R		R164E			E129R	H521R
		V538R	A390R		E167R			A311R	Q554R
		E539R	A413R					D313R	
								D337R	

*EC50 を減少させる

表３９．５　Table 39.5
EC50 シフトのヒット　Hit of EC50 shift
Bmax シフトのヒット　Hit of Bmax shift
*EC50 を減少させる　*Decrease EC50

B　Judgment

Corrected Invention 1 is "an isolated monoclonal antibody" specified by two constituent features of "capable of neutralizing the binding of PCSK9 and LDLR protein" and "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 in regard to the binding with PCSK9".

In contrast, the Detailed Description of the Invention discloses in details a method of preparing anti-PCSK9 monoclonal antibody (the above A(F)) and a method of competition assay (the above A(D)), and furthermore describes 23 kinds of antibodies 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 (BIN 1 of the above A(I), BINs 1 and 2 of (M)) in addition to their sequence information (the above A(G)). Further, it is well-known in general that an antibody competing with a reference antibody has a functional property similar to a reference antibody (the above A(D)), and actually 20 kinds of the above 23 kinds of competing antibodies were strong neutralizing antibodies and two kinds thereof were weak antibodies (the above A(H)). It is obvious from their screening processes (the above A(F)) that the neutralization used herein is a neutralization in a sense of "capable of neutralizing the binding of PCSK9 and LDLR".

As in the foregoing, the Detailed Description of the Invention describes plural kinds of specific antibodies encompassed into Corrected Invention 1, and a person ordinarily skilled in the art could recognize from the description of a method for preparing the same and a screening method that an antibody included into Corrected Invention 1 might be further obtained. Thus Corrected Invention 1 is described in the Detailed Description of the Invention over the whole range.

Further, it is theoretically (the above A(A)) and experimentally (the above A(K)) described that the antibodies of Corrected Invention 1 can be used as a pharmaceutical. Thus it can be said that Corrected Invention 9 also describes the Detailed Description of the Invention.

Therefore, Corrected Inventions 1 and 9 conform to the requirements under

Article 36(6)(i) of the Patent Act.

(3) Summary

As described above, the reasons for invalidation 1 is groundless.

2 Regarding Reasons for Invalidation 2 (nonconformance to enablement requirement)

(1) Details of Demandant's allegation

As pointed out in the Reasons for Invalidation 1, it is only 21B12 antibody, or only three groups of antibodies that specifically describes in the Detailed Description of the Invention from antibodies with various structures encompassed into Corrected Invention 1. In view of the common general knowledge that the substitution, addition or defect of only one amino acid in CDRs of heavy chain and light chain that are regions associated with the binding ability of antibodies may result in the loss of binding specificity of the original antibody, it is necessary to make trial and errors and conduct sophisticated experiment that go beyond the expectation by a person skilled in the art to make antibodies with various structures encompassed into Corrected Invention 1 on the basis of the above description.

Further, the competition with 21B12 antibody is always limited to excellent neutralizing ability. Thus it might include antibodies with significantly low non-neutralizing antibody and neutralizing ability in competing antibodies. It cannot be said that such antibody can be used for a desired purpose.

(2) Judgment by the body

As determined in the above 1(2)B, the Detailed Description of the Invention is described to the extent that allows a person skilled in the art to make and use the antibody according to Corrected Invention 1 and the pharmaceutical composition according to Corrected Invention 9.

Further, Demandant alleges that (A) the Detailed Description of the Invention describes only a few kinds of specific examples of antibodies encompassed into Corrected Invention 1. In view of the common technical knowledge that the CDR of antibody may lose its binding specificity by the substitution, addition or loss of only one amino acid, it cannot be said that the Detailed Description of the Invention is described so as to make antibody for the whole range of Corrected Invention 1, and that (B) the competition with 21B12 antibody does not necessarily result in the excellent neutralizing ability, and thus Corrected Invention 1 encompasses antibody having no or a significantly low neutralizing ability, and it cannot be said that such antibody may be used.

Regarding the above (A), as in the case of Example (the above 1(2)A(F)), monoclonal antibody with a desired property is usually obtained by screening various kinds of monoclonal antibodies obtained from an animal to which an antigen is administered, and the antibody thus obtained has an antigen-binding region with various structures generated by the recombination of antibody genes. Therefore, it is recognized that a person skilled in the art could prepare various antibodies encompassed into Corrected Invention 1 without reference to amino acid sequence of specific antibodies disclosed in the Detailed Description of the Invention. Thus the Demandant's allegation is not acceptable.

Further, regarding the above (B), Corrected Invention 1 comprises the constituent elements of "capable of neutralizing the binding of PCSK9 and LDLR protein" in addition to the competition with 21B12 antibody. Thus the Demandant's allegation is not reasonable.

(3) Summary

As described above, the reasons for invalidation 2 is groundless.

3 Regarding Reasons for invalidation 3 (violation of requirements for clarity)

Claim 5 of the Patent is canceled by the correction as per the above No. 2. Thus the reasons for invalidation 3 of the invention according to Claim 5 being indefinite is groundless.

4 Regarding Reasons for Invalidation 4 (Lack of inventive step)

(1) Described matters in Evidence A No. 1

Evidence A No. 1 (J. Clin. Invest., vol. 116(11), p.2995-3005 (Nov, 2006)) is an academic paper published before the priority date of the Patent and describes the following matters:

A "We show that purified PCSK9 added to the medium of HepG2 cells reduces the number of cell-surface LDLRs in a dose- and time-dependent manner. This activity was approximately 10-fold greater for a gain-of-function mutant, PCSK9(D374Y), that causes hypercholesterolemia. Binding and uptake of PCSK9 were largely dependent on the presence of LDLRs. Coimmunoprecipitation and ligand blotting studies indicated that PCSK9 and LDLR directly associate; ... To determine whether PCSK9 was active in plasma, transgenic PCSK9 mice were parabiosed with wild-type littermates. After parabiosis, secreted PCSK9 was transferred to the circulation of wild-type mice and reduced the number of hepatic LDLRs to nearly undetectable levels. We conclude that secreted PCSK9 associates with the LDLR and reduces hepatic LDLR protein levels." (page 2995, Abstract)

B "The biological activity of PCSK9 was revealed through overexpression studies in mice. Overexpression of PCSK9 posttranscriptionally reduced the amount of LDLR protein in liver Confirmation that PCSK9 functions normally to regulate LDLR protein levels came from loss-of-function studies in humans and mice. Individuals who are heterozygous for a nonsense mutation in allele PCSK9 have significantly lower plasma LDL cholesterol levels, suggesting that a reduction in PCSK9 activity leads to an increase in LDLRs These conclusions were supported by the studies of PCSK9 knockout mice, which revealed that loss of PCSK9 resulted in increased numbers of LDLRs in hepatocytes, accelerated plasma LDL clearance, and significantly lower plasma cholesterol levels. In the most recent studies, humans heterozygous for loss-of-function mutations in PCSK9 were shown to have a significant reduction in the long-term risk of developing atherosclerotic heart disease

The genetic data from humans and the in vivo studies in mice demonstrate that one function of PCSK9 is to reduce the number of the LDLRs and that this function is manifest in humans in the basal state." (page 2995, right column, lines 6 to 25)

C "The genetic data from humans with loss-of-function mutations in PCSK9 combined with the studies in knockout mice that lack PCSK9 clearly indicate that inhibitors of the protease would be of therapeutic benefit for the treatment of

hypercholesterolemia. ... If PCSK9 functions as a secreted factor as suggested by the current data, then additional approaches to neutralize its activity, including the development of antibodies to block its interaction with the LDLR or inhibitors to block its action in plasma, can be explored for the treatment of hypercholesterolemia." (page 3002, right column, lines 13 to 1 from the bottom)

D "Antibodies. For the anti-human PCSK9 polyclonal antibody, the human PCSK9 amino acid sequence was analyzed using Protean software for immunogenic regions. Amino acids 165-180 (RYRADEYQPPDGGSLV) and 220-240 (ASKCDSHGTHLAGVVSGRDAG) were synthesized, conjugated to keyhole-limpet hemocyanin using the Imject Maleimide Activated mcKLH kit (Pierce), and rabbits were injected with a mixture of the peptides as described previously. IgG fractions from sera were purified using the ImmunoPure (A/G) IgG purification kit (Pierce)." (page 3003, left column, lines 26 to 33)

(2) Judgment by the body

According to the above (1)A to C, Evidence A No. 1 provides a motivation to seek for a substance to inhibit the interaction of PCSK9 and LDLR for the purpose of developing a pharmaceutical for the treatment of hypercholesteremia. Further, as per described in the above (1)D, antibody is well-known as a substance inhibiting the interaction between biomolecules. Thus it can at least be said that a person skilled in the art could easily conceive of the preparation of antibody inhibiting the interaction between PCSK9 and LDLR.

Taking the common technical knowledge into account, however, a specific structure of "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 variable region consisting of the amino acid sequence of SEQ ID NO. 23" cannot be deduced from Evidence A No. 1, let alone "an antibody competing with" the antibody.

Therefore, it cannot be recognized that Corrected Inventions 1 and 9 were easily conceivable by a person ordinarily skilled in the art on the basis of Evidence A No. 1 and well-known technique. The reasons for Invalidation 4 is groundless.

5 A demand for trial with respect to the inventions according to Claims 2 to 8 of the Patent

Claims 2 to 8 of the Patent is canceled by the correction as per the above No. 2. As a result, a demand for trial with respect to the inventions according to Claims 2 to 8 lacks the subject, and is thus an illegal demand. No amendment to the demand can be made. Thus the demand for trial should be dismissed under the provision of Article 135 of the Patent Act.

No. 6 Closing

As described above,

Further, the patents according to Corrected Inventions 1 and 9 may not be invalidated on the basis of Demandant's allegation and means of proof.

Further, the inventions according to Claims 2 to 8 of the Patent are canceled by the correction. Thus the demand for trial made by Demandant with respect to these inventions should be dismissed.

The costs in connection with the trial shall be borne by Demandant under the

provisions of Article 61 of the Code of Civil Procedure as applied mutatis mutandis to the provision Article 169(2) of the Patent Act.

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

August 2, 2017

Chief administrative judge: TAMURA, Akiteru
Administrative judge: NAGAI, Keiko
Administrative judge: YAMAMOTO, Kyoko