United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LIMITED, AMGEN USA, INC.,
Plaintiffs-Appellants

v.

SANOFI, AVENTISUB LLC, FKA AVENTIS PHARMACEUTICALS INC., REGENERON PHARMACEUTICALS INC., SANOFI-AVENTIS U.S. LLC,
Defendants-Appellees

2020-1074

Appeal from the United States District Court for the District of Delaware in Nos. 1:14-cv-01317-RGA, 1:14-cv-01349-RGA, 1:14-cv-01393-RGA, 1:14-cv-01414-RGA, Judge Richard G. Andrews.

Decided: February 11, 2021

JEFFREY A. LAMKEN, MoloLamken LLP, Washington, DC, argued for plaintiffs-appellants. Also represented by SARAH JUSTINE NEWMAN, MICHAEL GREGORY PATTILLO, JR.; SARA MARGOLIS, New York, NY; ERICA S. OLSON, Amgen Inc., Santa Monica, CA; EMILY JOHNSON, STEVEN TANG, STUART WATT, WENDY A. WHITEFORD, Thousand Oaks, CA; KEITH HUMMEL, Cravath Swaine & Moore LLP, New York,

NY; WILLIAM G. GAEDE, III, McDermott, Will & Emery LLP, Menlo Park, CA; CHRISTOPHER B. MEAD, Schertler Onorato & Mead LLP, Washington, DC; JAMES L. HIGGINS, MELANIE K. SHARP, Young, Conaway, Stargatt & Taylor LLP, Wilmington, DE. Plaintiff-appellant Amgen Inc. also represented by SARAH CHAPIN COLUMBIA, McDermott, Will & Emery LLP, Boston, MA; LAUREN MARTIN, Quinn Emanuel Urquhart & Sullivan LLP, Boston, MA.

MATTHEW WOLF, Arnold & Porter Kaye Scholer LLP, Washington, DC, argued for defendants-appellees. Also represented by VICTORIA REINES; DAVID K. BARR, DANIEL REISNER, New York, NY; DEBORAH E. FISHMAN, Palo Alto, CA; GEORGE W. HICKS, JR., NATHAN S. MAMMEN, CALVIN ALEXANDER SHANK, Kirkland & Ellis LLP, Washington, DC. Defendants-appellees Sanofi, Aventisub LLC, Sanofi-Aventis U.S. LLC also represented by STEPHANIE DONAHUE, Sanofi, Bridgewater, NJ. Defendant-appellee Regeneron Pharmaceuticals Inc. also represented by LARRY A. COURY, LYNDA NGUYEN, Regeneron Pharmaceuticals Inc., Tarrytown, NY.

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STANLEY D. LIANG, Tarrytown, NY, as amicus curiae, pro se.

Before PROST, *Chief Judge*, LOURIE and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Amgen Inc., Amgen Manufacturing, Ltd., and Amgen USA, Inc. (collectively, "Amgen") appeal from a decision of the United States District Court for the District of Delaware granting Judgment as a Matter of Law ("JMOL") of lack of enablement of claims 19 and 29 of U.S. Patent 8,829,165 (the "'165 patent") and claim 7 of U.S. Patent 8,859,741 (the "'741 patent"). *See Amgen Inc. v. Sanofi*, No. CV 14-1317-RGA, 2019 WL 4058927, at *1–2, *13 (D. Del. Aug. 28, 2019) ("*Decision*"). For the reasons set forth below, we affirm.

BACKGROUND

Elevated low-density lipoprotein ("LDL") cholesterol is linked to heart disease. LDL receptors remove LDL cholesterol from the blood stream, thus regulating the amount of circulating LDL cholesterol. The proprotein convertase subtilisin/kexin type 9 ("PCSK9") enzyme regulates LDL receptor degradation. PCSK9 binds to LDL receptors and mediates their degradation, thus decreasing the number of LDL receptors on a cell's surface. Antibodies may bind to and block PCSK9, allowing LDL receptors to continue regulating the amount of circulating LDL cholesterol.

Amgen owns the '165 and '741 patents, which describe antibodies that purportedly bind to the PCSK9 protein and lower LDL levels by blocking PCSK9 from binding to LDL receptors. The '165 and '741 patents share a common written description. *See* Appellants' Br. 10 n.2. The specification discloses amino acid sequences for twenty-six antibodies, including the antibody (designated as "21B12")

with the generic name of evolocumab, marketed by Amgen as Repatha®. *See* '165 patent col. 85 ll. 1–43; Appellants' Br. 11 n.3. As shown for example in Figure 20A of the '165 patent, the specification discloses three-dimensional structures for the antibodies designated 21B12 and 31H4 and shows where those antibodies bind to PCSK9. The '165 and '741 patents claim antibodies that bind to one or more of fifteen amino acids (*i.e.*, "residues") of the PCSK9 protein and block PCSK9 from binding to LDL receptors.

The relevant '165 patent claims are:

> 1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
>
> 19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.
>
> 29. A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO: 3 and blocks the binding of PCSK9 to LDLR by at least 80%.

'165 patent col. 427 l. 47–col. 430 l. 23.

The relevant '741 patent claims are:

> 1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
>
> 2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.
>
> 7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

'741 patent col. 427 ll. 36–57. The claimed antibodies are defined by their function: binding to a combinations of sites (residues) on the PCSK9 protein, in a range from one residue to all of them; and blocking the PCSK9/LDLR interaction.

This is the second time that these patents have been on appeal in our court. Amgen filed suit against Sanofi, Aventisub LLC, Regeneron Pharmaceuticals Inc., and Sanofi-Aventis U.S. LLC (collectively, "Sanofi") on October 17, 2014, alleging infringement of multiple U.S. patents, including the '165 and '741 patents. *Decision* at *1. Amgen and Sanofi stipulated to infringement of selected claims (including '165 patent claims 19 and 29 and '741 patent claim 7) and tried issues of validity to a jury in March 2016. *Id.* During the trial, the district court granted JMOL of nonobviousness and of no willful infringement. *Id.* At the close of the trial, the jury determined that the patents were not shown to be invalid for lack of enablement and written description. *Id.*

Sanofi appealed to this court. Relevant to the current appeal, we held that the district court erred in its evidentiary rulings and jury instructions regarding Sanofi's defenses that the patents lack written description and enablement, and we remanded for a new trial on those

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