

UPC CFI, Central Division Munich, 16 July 2024,  
Sanofi-Aventis v Amgen



## PATENT LAW – PROCEDURAL LAW

Patent revoked because of lack of inventive step  
([Article 56 EPC](#))

- Starting from Lagace the skilled person having the aim to provide a treatment or way of prevention of [...] would as a next step have pursued the route of developing antibodies that block the interaction between PCSK9 and LDLR as explicitly suggested by Lagace [...] [and] would have ended up with antibodies as defined in the claims without inventive skill

Claim interpretation of a medical use product claim  
([Article 69 EPC](#))

- The relevant point in time for interpreting a patent claim for the assessment of validity is the filing (or priority) date of the application that led to the patent in suit.
- Medical use format claims ([Article 54\(4\)\(5\) EPC](#)) are purpose-limited product claims. The product specified in a medical use claim must be objectively suitable for the claimed use; it must be able to be used for the treatment, prevention or reduction as specified in the claim. In this sense, it must be therapeutically effective.

Skilled person is a team set out to solve a problem

- The skilled person in this case is a team including someone having a university degree in biological sciences (or biochemistry) and several years of (post-doctorate) experience in the field of antibody technology and a researcher with a number of years post-doctorate research experience who is undertaking preclinical research into the treatment of cardiovascular diseases, and who has an interest in PCSK9 biology with respect to the role and function of PCSK9 in regulating LDL levels
- The skilled person who, as rightly pointed out by the Defendant, is not an academic wishing to explore and understand the PCSK9 mechanism, but is a team that is set out to solve a problem, will consider a prior art document in its entirety in light of their common

general knowledge and make realistic and practical deductions from a prior art teaching.

- The skilled person is aiming to solve a problem and in doing so is considering which next step(s), if any, are realistically to be taken. Absent any apparent errors or omissions in a prior art document, a skilled person will not be overly cautious (nor creative) and does not analyse every experiment in a prior art document in isolation with a view to the questions it does not answer but will rather be inclined to accept published (and peer reviewed) research results and reasonable conclusions drawn from those results at face value.

Interpretation of the claims ([Article 69 EPC](#))

- The meaning of the term “catalytic domain” is not explicitly defined in the Patent. The catalytic domain is understood by the skilled person as the region consisting of amino acid residues 123 to 419 of human PCSK9 (SEQ ID NO: 1)

Based on wording of the claim and the description. It follows from the above that Figure 26 does not contain the “sole definition” of the catalytic domain

- Feature F.3 should not be considered in isolation; its meaning must be determined in light of the claim as a whole and the underlying problem.

In particular, features F.4 (and F.2) must also be considered. The skilled person recognises that the binding of the antibody required in F.3 is intended to have a **consequence**. Namely that which is mentioned in F.4: the antibody is intended to **prevent or reduce the binding of PCSK9 to LDLR**.

- The skilled person will therefore understand any binding which also takes place in the catalytic domain and which fulfils this technical purpose - preventing or reducing the binding of PCSK9 to LDLR - to suffice.
- In view of the teaching of the Patent as a whole, the skilled person would understand the claimed treatment not to be limited to a particular lowering of cholesterol levels as long as there is some (measurable) reduction of cholesterol levels in vivo and provided the therapy is safe.

The Central Division furthermore notes that the claimed use encompasses the administration of the claimed antibodies together with at least one other cholesterol-lowering agent, notably statins (claims 6 and 7 of the Patent). This confirms the understanding of the skilled person that also a (very) small cholesterol-lowering effect caused by the claimed antibodies can be “therapeutically effective” in the sense of the claimed treatments.

- Claimed antibodies: patentee has chosen broader claim wording instead of defining the claimed antibodies in a narrower way

- not all antibodies that may conceivably bind to the catalytic domain are covered by the claim  
- antibodies that do not bind to the catalytic domain (but exclusively to the pro- or V-domain) are not covered by the claims.

Thus, F.3, F.4 and F.2 indeed limit the number of antibodies falling under the claim.

- the claims are not limited to antibodies which, like “reference antibodies” 21B12 and 31H4, are able to directly or sterically block PCSK9 from binding to LDLR by binding to or near residues that overlap with the EGFA binding region of PCSK9 (...).

- For the skilled person, it will appear that the patentee has chosen the present broader claim wording instead of defining the claimed antibodies in a narrower way.

**Priority: “same invention” requirement (Article 87 EPC)**

• a claimed invention is to be considered the same invention as the invention in a previous application if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole (cf. EPO Enlarged Board of Appeal 31 May 2001, G2/98, ECLI:EP:BA:2001:G000298.20010531).

**Claimed subject matter is obvious and does not involve an inventive step (Article 56 EPC)**

• An objective approach must be taken to the assessment of inventive step. The subjective ideas of the applicant or inventor are irrelevant. In principle, it is also irrelevant whether the invention is the result of serendipity or of systematic work involving (potentially costly and laborious) experimentation. It is only relevant what the claimed invention actually contributes to the prior art.

• Any starting point that has the same underlying problem as the claimed invention is a realistic starting point

It is first necessary to determine a starting point in the state of the art. There has to be a justification as to why the skilled person would consider a particular part of the state of the art as a realistic starting point. A starting point is realistic if its teaching would have been of interest to a skilled person who, at the priority date of the patent at issue, was seeking to develop a similar product or method to that disclosed in the prior art which thus has a similar underlying problem as the claimed invention (cf. Court of Appeal Nanostring/10x Genomics, p. [...]). There can be several realistic starting points. It is not necessary to identify the “most promising” starting point

• In general, a claimed solution is obvious if, starting from the prior art, the skilled person would be motivated (i.e. have an incentive or in German: “Veranlassung”, see the CoA in NanoString/10x Genomics, p. 34) to consider the claimed solution and to implement it as a next step (“nächster Schritt”, CoA in NanoString/10x Genomics, p. 35, second par.) in developing the prior art. On the other hand, it may be relevant whether the skilled person would have expected any particular difficulties in taking any next step(s).

• Depending on the facts and circumstances of the case, it may be allowed to combine prior art disclosures.

• A technical effect or advantage achieved by the claimed subject matter compared to the prior art may be an indication for inventive step.

• A feature that is selected in an arbitrary way out of several possibilities cannot generally contribute to inventive step.

• Hindsight needs to be avoided. The question of inventive step should not be answered by searching retrospectively, with knowledge of the patented subject matter or solution, for any (combination) prior art disclosures from which that solution could be deduced.

• Starting from Lagace the skilled person having the aim to provide a treatment or way of prevention of [...] would as a next step have pursued the route of developing antibodies that block the interaction between PCSK9 and LDLR as explicitly suggested by Lagace [...] [and] would have ended up with antibodies as defined in the claims without inventive skill.

8.31 The Central Division finds that the skilled person having the aim to, starting from Lagace, provide a treatment or way of prevention of hypercholesterolaemia or atherosclerotic disease associated with elevated serum cholesterol levels or for use in reducing the risk of recurrent cardiovascular events associated with elevated serum cholesterol levels targeting PCSK9 to regulate levels of LDLRs (and thereby LDL), would as a next step have pursued the route of developing antibodies that block the interaction between PCSK9 and LDLR as explicitly suggested by Lagace. Pursuing that route the skilled person would have ended up with antibodies as defined in the claims without inventive skill.

• Left undecided whether a reasonable expectation of success is required

8.56 The Central Division can leave undecided the question of whether or not under the circumstances of the present case, where there is an incentive in the prior art towards the claimed subject matter and the next steps would not amount to more than routine experimentation for the skilled person, a reasonable expectation of success is required to come to the conclusion that the claimed subject matter lacks inventive step. In the present case, the Defendant has not put forward any (technical) problems that the person skilled in the art would not have been able to overcome on the basis of their common general knowledge at the relevant date. The uncertainties raised by the Defendant would not have prevented the skilled person from taking the obvious next step, i.e. developing PCSK9/LDLR inhibiting antibodies to treat hypercholesterolemia and related disorders, due to insufficient prospects of success (cf. the CoA in NanoString/10x Genomics, p.36 second par.).

• The absence of a reasonable expectation of success (or more in general: nonobviousness) does not follow from the mere fact that other ways of solving the underlying problem are also suggested in the prior art and/or (would) have been pursued by others.

• Requiring considerable time and resources does not constitute an “undue burden” in patent law terms

The skilled person would have realised that making antibodies and setting up the screening methods may require considerable time and resources, but to do so does not constitute an “undue burden” in patent law terms.

- **That the inventors took a non-routine approach to obtain the functional antibodies does not mean that the skilled person would not arrive at such an antibody using routine methods.**

8.74 Furthermore, even if it were accepted in favour of the Defendant that the inventors of the Patent took a non-routine approach and obtained the results (functional antibodies) included in the Patent, this does not mean that the skilled person would not arrive at an antibody falling under the scope of the Patent claims using routine methods of antibody generation and selection as the Claimants have credibly argued supported by references to the common general knowledge (see e.g. 3.2.8 CC, 2.11 Case Summary) and as also follows from the above discussion.

## PROCEDURAL LAW

### Application to amend (auxiliary requests) (**Rule 30 RoP, Rule 50 RoP**)

- **Rule 30 RoP applies mutatis mutandis in a revocation action based on Rule 50 RoP.**

Source: **Unified Patent Court**

See for the (in substance identical) decision of the same date in **Regeneron v Amgen**: **Unified Patent Court**

### UPC Court of First Instance, Central Division (Section Munich), 16 July 2024

(Vos, Kupecz, Struve)

UPC\_CFI\_1/2023

#### Decision

of the Court of First Instance of the Unified Patent Court delivered on 16 July 2024 concerning **EP 3 666 797 B1**

#### HEADNOTES:

1. *When interpreting a patent claim, the person skilled in the art does not apply a philological understanding, but determines the technical meaning of the terms used with the aid of the description and the drawings. From the function of the individual features in the context of the patent claim as a whole, it must be deduced which technical function these features actually have individually and as a whole. The patent description may represent a patent’s own lexicon.*

2. *A claimed invention is to be considered the “same invention” as meant in **Article 87 EPC** (priority right) if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.*

3. *The assessment of inventive step starts from a realistic starting point in the prior art. There can be several realistic starting points. It is not necessary to identify the “most promising” starting point.*

4. *In general, a claimed solution is obvious if the skilled person would be motivated to consider the claimed solution and would implement it as a next step in developing the prior art. It may be relevant whether the skilled person would have expected any particular difficulties in taking any next step(s). The absence of a reasonable expectation of success (or more in general: non-obviousness) does not follow from the mere fact that other ways of solving the underlying problem are also suggested in the prior art and/or (would) have been pursued by others. The decisive question that has to be answered is whether the claimed solution is non-obvious.*

5. *For assessing inventive step it is not the question whether the skilled person would inevitably arrive at the same result (falling within the scope of the claim or not). Rather, it is sufficient (but also necessary) for denying inventive step that the skilled person would without inventive contribution arrive at a result which is covered by a claim.*

6. *A technical effect or advantage achieved by the claimed subject matter compared to the prior art may be an indication for inventive step. A feature that is selected in an arbitrary way out of several possibilities cannot generally contribute to inventive step.*

#### KEYWORDS:

*Revocation, claim interpretation, priority, inventive step, starting point, obviousness, inventive contribution, arbitrary selection out of several possibilities*

**IN CASE 459505/2023 (UPC\_1/2023)**

#### CLAIMANTS

1) **Sanofi-Aventis Deutschland GmbH**, Brüningstrasse 50 - 65926 - Frankfurt - DE

2) **Sanofi-Aventis Groupe** - 82 Avenue Raspail - 94250 - Gentilly - FR

3) **Sanofi Winthrop Industrie S.A.** (Claimant) - 82 Avenue Raspail - 94250 - Gentilly - FR

(also collectively referred to as “the Claimants”) represented by Agathe Michel-de Cazotte, Daniel Wise (Carpmaels & Ransford) also at the hearing by: Emily Nikolić (Carpmaels & Ransford) and Gregor König (König - Szyuka - Tilmann - Von Renesse).

#### DEFENDANT:

**Amgen, Inc.** (Defendant) - One Amgen Center Drive - CA 91320-1799 - Thousand Oaks - US

Represented by Koen Bijvank (Brinkhof) also at the hearing by: Daan de Lange, Rik Lambers, Jonathan Santman, Roza Rijpkema (Brinkhof), Johannes Heselberger and Axel Berger (Bardehle Pagenberg) and H. Ulrich Dörries (df-mp).

#### PATENT AT ISSUE

European patent **EP 366 6797 B1**, hereafter referred to as “EP 797” or as “the Patent”.

#### PANEL/DIVISION

Panel 1 of the Central Division (Section Munich).

#### DECIDING JUDGES

This decision has been delivered by the presiding judge Ulrike Voß, the legally qualified judge Andrés Kupecz as judge-rapporteur and the technically qualified judge Casper Struve..

#### DATE OF THE ORAL HEARING



4 June 2024

## SUMMARY OF FACTS AND REQUESTS

### 1 Background of the dispute

1.1 The Claimants and the Defendant both market cholesterol-lowering antibody drugs which are biotechnologically produced PCSK9 inhibitors. The Claimants' drug is sold under the trade name Praluent®, whereas the Defendant sells a cholesterol-lowering drug under the trade name Repatha®. Several proceedings between the parties are pending at the Unified Patent Court ("UPC") and elsewhere.

1.2 On 1 June 2023, the Claimants brought the present revocation action against the Patent in the Central Division (Section Munich) of the UPC (ACT\_459505/2023 UPC\_CFI\_1/2023, "the Revocation action").

1.3 On 1 June 2023, Defendant brought an infringement action related to the Patent to the Munich Local Division of the UPC against the Claimants and Regeneron Pharmaceuticals, Inc. This action is pending under number ACT\_459916/2023. In the infringement action, a counterclaim for revocation of the Patent was filed by Regeneron Pharmaceuticals Inc., but not by the Claimants. The counterclaim was served on 24/11/2023 and has been assigned number CC\_586764/2023 ("the Counterclaim"). By [order dated 2 February 2024 \(ORD 392/2024\)](#), the Local Division Munich, with the agreement of the parties, referred the Counterclaim of Regeneron to the Central Division.

1.4 After the referral of the Counterclaim, the Central Division ordered that the Revocation action and the Counterclaim were to be dealt with jointly. Details of the instructions to the parties are included in the Order to combine the cases dated [27 February 2024 which is hereby referred to \(Order no. ORD 10396/2024 in ACT 459505/2023 and Order no. ORD 10398/2024 in CC 586764/2023, respectively\)](#). All facts, grounds, arguments and evidence exchanged are known to all parties and are accepted as submitted by the Claimants in both cases, all pleadings and applications (including the application to amend/auxiliary requests) are also deemed to have been submitted in both actions and all exhibits (and evidence) are deemed to have been filed in and are part of both actions. In this decision, the numbering of exhibits as used in the Revocation Action is used, unless explicitly indicated otherwise.<sup>1</sup>

1.5 The oral hearing in actions ACT\_459505/2023 and CC\_586764/2023 was held jointly on 4 June 2024. The (in substance identical) decisions in both actions are issued and read in open court today, 16 July 2024.

1.6 For the submissions of the parties and previous orders issued by the Court, reference is made to the case file in the Case Management System.

### 2 The Patent

2.1 The Patent entitled "ANTIGEN BINDING PROTEINS TO PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)" was filed on

**22 August 2008** (application as filed WO 2009/026558, A1). The Patent claims priority to US20070957668P (P1, 23.08.2007), US20070008965P (P2, 21.12.2007), US20080010630P (P3, 09.01.2008) and US20080086133 (P4, 04.08.2008).

2.2 The Patent derives from a European (multigenerational) divisional patent application (EP 19207796.4). The application is ultimately derived from PCT application PCT/US2008/074097, which was filed on 22 August 2008, published as WO2009/026558 (A1), and entered the European regional phase as EP Application No. 08798550.3 (granted as EP 2 215 124).

2.3 The publication of the mention of the grant of the Patent was made on 17 May 2023. Registered owner of the Patent is the Defendant.

2.4 Opposition against the grant of the Patent at the European Patent Office ("EPO") was lodged by Sanofi-Aventis Deutschland GmbH on 10 November 2023 and by Regeneron Pharmaceuticals Inc. on 19 February 2024.

2.5 The Patent is in force in the UPC Contracting Member States Austria (AT), Belgium (BE), Bulgaria (BG), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Germany (DE), Italy (IT), Latvia (LV), Lithuania (LT), Luxembourg (LU), Malta (MT), The Netherlands (NL), Portugal (PT), Slovenia (SI) and Sweden (SE). 2.6 The claims of the Patent as granted read:

1. *A monoclonal antibody or an antigen-binding fragment thereof for use in treating or preventing hypercholesterolemia or an atherosclerotic disease related to elevated serum cholesterol levels; or for use in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels; wherein the monoclonal antibody or the antigen-binding fragment thereof binds to the catalytic domain of a PCSK9 protein of the amino acid sequence of SEQ ID NO: 1, and prevents or reduces the binding of PCSK9 to LDLR.*
2. *The monoclonal antibody or the antigen-binding fragment thereof for use according to claim 1, in treating or preventing hypercholesterolemia.*
3. *The monoclonal antibody or the antigen-binding fragment thereof for use according to claim 1, in treating or preventing an atherosclerotic disease related to elevated serum cholesterol levels.*
4. *The monoclonal antibody or the antigen-binding fragment thereof for use according to claim 3, wherein the atherosclerotic disease is selected from coronary heart disease, coronary artery disease, peripheral arterial disease, ischaemic or hemorrhagic stroke, angina pectoris, cerebrovascular disease, acute coronary syndrome, or myocardial infarction.*
5. *The monoclonal antibody or the antigen-binding fragment thereof for use according to claim 1, wherein*

<sup>1</sup> The Statement of Revocation, Defence to Revocation, Reply to the Defence to Revocation and Rejoinder to the Reply to the Defence to Revocation in case 459505/2023 are herein referred to as 'SR', 'DtR', 'Rtd' and 'R', respectively. The counterclaim for revocation in

CC 586764/2023 is referred to as 'CC' and the Defence to the Counterclaim as 'DtCC'. The parties each made a further submission in CC\_586764/2023, referred to as 'RtdCC' and 'RCC', respectively.

*the monoclonal antibody or the antigen-binding fragment thereof is for use in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels.*

*6. The monoclonal antibody or the antigen-binding fragment thereof for use according to any one of claims 1 to 5, wherein the monoclonal antibody or antigen-binding fragment thereof is administered together with at least one other cholesterol-lowering agent.*

*7. The monoclonal antibody or the antigen-binding fragment thereof for use according to claim 6, wherein the at least one other cholesterol-lowering agent is a statin, optionally wherein the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.*

*8. The monoclonal antibody or the antigen-binding fragment thereof for use according to any one of claims 1 to 7, wherein the monoclonal antibody or the antigen-binding fragment thereof is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a Fab fragment, an F(ab)2 fragment, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody or an antigen-binding fragment thereof.*

*9. The monoclonal antibody or the antigen-binding fragment thereof for use according to any one of claims 1 to 8, wherein the monoclonal antibody or the antigen-binding fragment thereof binds to a PCSK9 variant that has a D374Y point mutation.*

*10. The monoclonal antibody or the antigen-binding fragment thereof for use according to any one of claims 1 to 9, wherein the monoclonal antibody or the antigen-binding fragment thereof binds to PCSK9 with a Kd that is smaller than 1 nM, is smaller than 100 pM, is smaller than 10 pM, or is less than 5 pM.*

*11. The monoclonal antibody or the antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the subject is a human patient.*

### 3 Requests

3.1 The Claimants argue that the Patent has been amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 138(1) sub c in connection with Article 123(2) of the European Patent Convention (“EPC”)), the invention is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 138(1) sub b in connection with Article 83 EPC), is not new (Article 138(1) sub a in connection with Article 54 EPC) and/or does not involve an inventive step (Article 138(1) sub a in connection with Article 56 EPC).

3.2 The Claimants request (as clarified during the oral hearing) that the Court:

- EP 3 666 797 be revoked with effect to the territory of Austria (AT), Belgium (BE), Bulgaria (BG), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Germany (DE), Italy

(IT), Latvia (LV), Lithuania (LT), Luxembourg (LU), Malta (MT), The Netherlands (NL), Portugal (PT), Slovenia (SI) and Sweden (SE).

- orders that the Defendant pays all costs incurred by the Claimants as per Article 69 of the Agreement on a Unified Patent Court (“UPCA”).

and:

- dismisses the Defendant’s Application to amend the Patent, as the amendments are not allowable and the Patent in suit cannot be maintained as requested in Auxiliary Requests (AR) 1-17.

3.3 The Defendant has put forward various defences including a (conditional) application to amend the Patent which was lodged together with the Defence to Revocation.

3.4 Defendant requests (as clarified during the oral hearing) that:

- the Revocation Action be rejected as being unfounded and the Patent be maintained as granted (Main Request; or “MR”); or failing that
- the Revocation Action be dismissed as being unfounded and the Patent be maintained on the basis of any of Auxiliary Requests (ARs) 1-17;
- the Claimants be ordered to pay Defendant’s costs.

3.5 The grounds and defences as brought forward by the parties will, to the extent relevant for this decision, be discussed in detail below

## GROUND FOR THE DECISION

### 4 Summary of the Outcome

4.1 The Central Division comes to the conclusion that the Patent as granted is invalid because it does not involve an inventive step over Lagace. Auxiliary Requests 1-17 lack inventive step for the same reasons. The skilled person who was interested in developing a treatment for hypercholesterolemia targeting PCSK9 would, starting from and following the teaching of Lagace, without inventive skill develop antibodies against PCSK9 that block the interaction of PCSK9 with the LDLR and would thereby arrive at the claimed subject matter in an obvious way.

### 5 Technical introduction

#### Antibodies

5.1 An antibody is a type of protein (also called an immunoglobulin, “Ig”) that is produced by the immune system in response to a foreign substance. Each antibody recognizes a particular target, also referred to as an “antigen”. Like all proteins, antibodies are made up of amino acids. Each amino acid has distinct chemical and physical properties. The amino acid sequence of an antibody is a major factor affecting how the antibody protein will fold into a three-dimensional structure, which in turn helps to determine which antigen or antigens the protein can bind, and how the antibody functions.

5.2 Each antibody is made up of two pairs of identical polypeptide chains (chains of amino acids linked together by peptide bonds) that form a flexible Y shape.

Each pair comprises a heavy chain polypeptide (the green segments depicted in the figure below) and a light chain polypeptide (the blue segments depicted in the figure below) that are held together by disulfide bonds (“-SS-” in the figure). Each polypeptide chain, light or heavy, has a “constant” and a “variable” domain. The ordering of amino acids in the heavy and light chain protein sequences of an antibody is encoded by the heavy and light chain genes for that antibody.

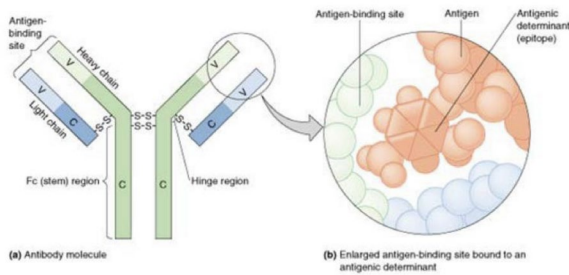


Figure 4 in the CC.

5.3 The variable domains are referred to as such because the amino acid sequence in these domains differs between antibodies. The variable domains make up the antigen-binding sites of an antibody, with each of the two antigen-binding sites within a particular antibody being identical.

5.4 The epitope is the region of an antigen that is bound by an antibody. When the antigen is a protein, the binding of an antibody to its antigen occurs via interactions between the amino acid residues on the antibody and the amino acid residues on the antigen.

5.5 As of the earliest priority date of the Patent in 2007, methods of making antibodies were well-established.

5.6 For example, antibodies can be made by immunizing mice. That involves immunizing mice with the desired target antigen, harvesting the mice, collecting the antibody-producing mouse B cells and fusing them with “immortal” cells to create “hybridomas.” Antibodies generated by the mouse immune system are then collected from the hybridomas for screening, each hybridoma cell producing a single antibody.

5.7 Alternatively, a method called phage display could be used in which an antibody sequence is presented on the surface of a bacteriophage. By repeating this process, one is able to produce many millions of bacteriophages each presenting a different antibody variable region that form a “library.” This library can then be screened for binding to a target antigen of interest. Other display techniques were also available. For example, yeast display is a method in which the antibody variable region sequences are expressed on the surface of yeast cells, one antibody per cell.

5.8 Another technique developed in the 1990s and described in the Patent involves generating transgenic mice by replacing that part of the mouse genome carrying the antibody genes with the human counterpart. When interrogated with the target protein of interest, these transgenic mice make human rather than murine

antibodies to the target protein. Background section of the Patent: PCSK9 and cholesterol

5.9 The Patent relates to antigen binding proteins that bind to proprotein convertase subtilisin kexin type 9 (“PCSK9”) and methods of using and making the antigen binding proteins.

5.10 As regards the background to the invention, the Patent initially states that PCSK9 is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein (para. [0002]). LDLR is a protein receptor expressed on the surface of liver cells that is important for removing Low density lipoprotein cholesterol (LDL-C), which is transported by Low density lipoprotein (LDL) throughout the body. Typically, LDLRs on the cell surface bind to LDL-C, transport LDL-C into the cell where it is broken down for the use by the body, and are then recycled to the cell where they can continue transporting LDL-C from the bloodstream into the cell.

5.11 Still according to the background section of the Patent, in vitro experiments had shown that adding PCSK9 to HepG2 cells lowers the levels of cell surface LDLR. Experiments with mice had shown that increasing PCSK9 protein levels decreases levels of LDLR protein in the liver, while PCSK9k knockout mice have increased levels of LDLR in the liver. Additionally, various human PCSK9 mutations that result in either increased or decreased levels of plasma LDL had been identified. PCSK9 had been shown to directly interact with the LDLR protein, be endocytosed along with the LDLR, and to co-immunofluoresce with the LDLR throughout the endosomal pathway.

5.12 Moreover, according to the background section of the Patent, it had been found that PCSK9 binds to the EGFA domain within the LDLR, referencing Zhang et al., 2007 (submitted as C4 in these proceedings). As the Patent further states, degradation of the LDLR by PCSK9 had not been observed and the mechanism through which it lowers extracellular LDLR protein levels is uncertain. Selective inhibition of the PCSK9 gene in hyperlipidemic mice using an antisense oligonucleotide (ASO) resulted in significant reductions in hepatic PCSK9 mRNA levels, with concomitant reductions in total cholesterol and LDL (para. [0002]).

5.13 The Patent explains as further background that PCSK9 is a prohormoneproprotein convertase in the subtilisin (S8) family of serine proteases (para. [0003]). Prohormone-proprotein convertases are expressed as zymogens and they mature through a multistep process. Humans have nine prohormoneproprotein convertases. Crystal and NMR structures of different domains from mouse furin and PC1 revealed subtilisin-like pro- and catalytic domains, and a P domain directly C-terminal to the catalytic domain. Based on the amino acid sequence similarity within this subfamily, all seven members were predicted to have similar structures.

5.14 Prohormone-proprotein convertases are expressed as zymogens and they mature through a multi-step process. The function of the pro-domain in this process is two-fold. The pro-domain first acts as a chaperone and is required for proper folding of the catalytic domain.



Once the catalytic domain is folded, autocatalysis occurs between the pro-domain and catalytic domain. Following this initial cleavage reaction, the pro-domain remains bound to the catalytic domain where it then acts as an inhibitor of catalytic activity. When conditions are correct, maturation proceeds with a second autocatalytic event at a site within the pro-domain. After this second cleavage event occurs the pro-domain and catalytic domain dissociate, giving rise to an active protease (para. [0004]).

5.15 Finally, the background section of the Patent explains that autocatalysis of the PCSK9 zymogen occurs between Gln152 and Ser153 (VFAQ|SIP), and had been shown to be required for its secretion from cells. A second autocatalytic event at a site within PCSK9's pro-domain had not been observed. Purified PCSK9 is made up of two species that can be separated by nonreducing SDS-PAGE; the pro-domain at 17 Kd, and the catalytic plus C-terminal domains at 65 Kd. PCSK9 has not been isolated without its inhibitory pro-domain, and measurements of PCSK9's catalytic activity have been variable (para. [0005] of the Patent description).

5.16 Against the above-mentioned background, the Patent does not formulate a concrete underlying problem. Notwithstanding, it can be deduced from the Patent description as a whole that the aim of the Patent is to provide a treatment or prevention of hypercholesterolaemia or atherosclerotic disease associated with elevated serum cholesterol levels or for use in reducing the risk of recurrent cardiovascular events associated with elevated serum cholesterol levels targeting PCSK9 to regulate levels of LDLRs (and thereby LDL).

5.17 In order to achieve this aim, the Patent claims the use of a monoclonal antibody or an antigen-binding fragment thereof having the features as discussed below.

## 6 Claim interpretation

6.1 Claim 1 can be divided into the following features:

*F1. A monoclonal antibody or an antigen-binding fragment thereof*

*F.2 for use*

*F2.1 in treating or preventing hypercholesterolemia or an atherosclerotic disease related to elevated serum cholesterol levels;*  
*or*

*F2.2 in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels.*

*F3. The monoclonal antibody or the antigen-binding fragment thereof binds to the catalytic domain of a PCSK9 protein of the amino acid sequence of SEQ ID NO: 1.*

*F4. The monoclonal antibody or the antigen-binding fragment thereof prevents or reduces the binding of PCSK9 to LDLR.*

6.2 In view of the debate between the parties, several features of claim 1 of the Patent require interpretation.

### Legal framework

6.3 The Court of Appeal of the UPC has laid down the following legal framework for the interpretation of patent claims (Order dated 26 February 2024 in UPC CoA 335/2023, NanoString/10x Genomics, p. 26-27 of the original German language version, also see CoA UPC 13 May 2024, VusionGroup/Hanshow).

6.4 In accordance with Art. 69 EPC and the Protocol on its interpretation, a patent claim is not only the starting point, but the decisive basis for determining the scope of protection of a European patent. The interpretation of a patent claim does not depend solely on the strict, literal meaning of the wording used. Rather, the description and the drawings must always be used as explanatory aids for the interpretation of the patent claim and not only to resolve any ambiguities in the patent claim. However, this does not mean that the patent claim merely serves as a guideline and that its subject-matter also extends to what, after examination of the description and drawings, appears to be the subject-matter for which the patent proprietor seeks protection.

6.5 The patent claim is to be interpreted from the point of view of a person skilled in the art.

6.6 When interpreting a patent claim, the person skilled in the art does not apply a philological understanding, but determines the technical meaning of the terms used with the aid of the description and the drawings. A feature in a patent claim is always to be interpreted in light of the claim as a whole (CoA UPC 13 May 2024, VusionGroup/Hanshow, point 29). From the function of the individual features in the context of the patent claim as a whole, it must be deduced which technical function these features actually have individually and as a whole. The description and the drawings may show that the patent specification defines terms independently and, in this respect, may represent a patent's own lexicon. Even if terms used in the patent deviate from general usage, it may therefore be that ultimately the meaning of the terms resulting from the patent specification is authoritative.

6.7 In applying these principles, the aim is to combine adequate protection for the patent proprietor with sufficient legal certainty for third parties

6.8 As held by the Court of Appeal, these principles apply also to the assessment of validity. Accordingly, these principles will also be applied by the Central Division to claim construction in the context of the present revocation action. The relevant point in time for interpreting a patent claim for the assessment of validity is the filing (or priority) date of the application that led to the patent in suit.

### The skilled person

6.9 The parties have not taken a firm position as to the identity of the skilled person. In the opinion of the Central Division, the skilled person in this case is a team including someone having a university degree in biological sciences (or biochemistry) and several years of (post-doctorate) experience in the field of antibody technology. The team also includes a researcher with a number of years post-doctorate research experience who is undertaking preclinical research into the treatment of cardiovascular diseases, and who has an interest in

PCSK9 biology with respect to the role and function of PCSK9 in regulating LDL levels (cf. 4.3 Case Summary Defendant, and E5, par. 18).

#### *Claim interpretation from the point of view of the skilled person*

6.10 The claims of the Patent are drafted in the so-called “medical use” format (“product X for use in treatment Y”) in accordance with [article 54\(4\)/\(5\) EPC](#). Such claims are to be regarded as purpose-limited product claims. The “product” in the claims of the Patent is characterised by features F.1, F.3 and F.4. Its medical use (the “purpose”) is specified in F.2, i.e. treating or preventing hypercholesterolemia or an atherosclerotic disease related to elevated serum cholesterol levels or in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels. The product specified in a medical use claim must be objectively suitable for the claimed use; it must be able to be used for the treatment, prevention or reduction as specified in the claim. In this sense, it must be therapeutically effective.

6.11 As follows from the technical introduction part above, the skilled person knows from their [common general knowledge](#) what a (monoclonal) antibody or fragment thereof is. The monoclonal antibody or fragment thereof (F.1) claimed (for the various medical uses) in the claims of the Patent is not further characterised where it concerns its amino acid sequence, (three-dimensional) structure or further (chemical) composition. In particular, the feature does not contain any requirements for the production of or specific methods of obtaining the antibody or antigen-binding fragment thereof. The description mentions multiple ways of obtaining antibodies. It was common general knowledge that antibodies can be produced using various methods. The skilled person therefore understands that the claim covers antibodies made using any such method. The antibody is (only) characterised in more detail by means of (functional) features F.3 and F.4 and its uses (F.2).

6.12 F.3 requires that the monoclonal antibody or fragment thereof “binds to the catalytic domain of a PCSK9 protein of the amino acid sequence of SEQ ID NO: 1” (F.3). This feature requires that the antibody binds to a particular area/region on PCSK9, namely the catalytic domain. The meaning of the term “catalytic domain” is not explicitly defined in the Patent. The catalytic domain is understood by the skilled person as the region consisting of amino acid residues 123 to 419 of human PCSK9 (SEQ ID NO: 1).

6.13 This understanding is first of all based on the wording of the claim. A “domain” in a protein is generally understood to be a distinct region of a protein, comprising multiple, such as several hundred, amino acid residues. A “catalytic” domain is generally understood to mean a region of a protein in which a catalytic reaction takes place. As described in the background section discussed above, the skilled person

knew that in prohormone-proprotein convertases, like PCSK9, the pro-domain acts as a chaperone and is required for a proper folding of the catalytic domain. Once the catalytic domain is folded, autocatalysis occurs in the catalytic domain where it then acts as an inhibitor of catalytic activity (par. [0004]). From this, the skilled person understands that the catalytic domain is the area/region of PCSK9 which contains the amino acids that are responsible for PCSK9’s (auto)catalytic cleavage.

6.14 Par. [0146] of the description confirms that the full length PCSK9 protein includes a signal sequence, an N-terminal pro-domain, a subtilisin-like catalytic domain and a C-terminal domain. SEQ ID NO:3 represents an exemplary full length human PCSK9 protein including the signal sequence. Par. [0005] of the Patent describes that autocatalysis of PCSK9 occurs between amino acid residues Gln152 and Ser153 (VFAQ/SIP).<sup>2</sup> The skilled person recognises that the amino acid numbering in par. [0005] still includes the 30 amino acid long signal sequence (as in SEQ ID NO:3, see Fig 1B, showing the signal sequence in bold). As explained in par. [0255] of the description of the Patent, SEQ ID NO:3 corresponds to SEQ ID NO:1, whereby SEQ ID NO:1 lacks the signal sequence. Accordingly, in Figure 1A the underlining of the pro-domain ends at Gln (“Q”) 122 (cf. par. [0058] of the description). The skilled person thus understands from the description that the pro-domain of PCSK9 ends at Gln122 and, accordingly, that the catalytic domain of PCSK9 starts at Ser123 of human PCSK9 (SEQ ID NO: 1).

6.15 Example 27 (describing a method for determining where various antibodies bind to PCSK9) distinguishes between a “ProCat” sequence (amino acid residues 31-449 of SEQ ID NO: 3) and the “V-domain” (another name for the “C-terminal domain”) sequence (amino acid residues 450-692 of SEQ ID NO: 3). Example 40, which also describes an experiment to investigate where on PCSK9 the various ABPs (NB. Antigen Binding Proteins, a term used throughout the description which includes monoclonal antibodies and fragments thereof) bound, equally distinguishes between full length PCSK9 (amino acids 31-692 of SEQ ID NO: 3), ProCat PCSK9 (amino acids 31-449 of SEQ ID NO: 3) and the V-domain (amino acids 450-692 of SEQ ID NO: 3). From this information, the skilled person will derive that term “catalytic domain”, as used in the Patent, ends at the last amino acid residue of the ProCat construct, before the V-domain starts, i.e. at amino acid residue 449 of SEQ ID NO: 3, corresponding to amino acid residue 419 of SEQ ID NO: 1 (in which the signal sequence is lacking, see above). This understanding is consistent with Figure 26 of the Patent in which the catalytic domain of PCSK9 is depicted as the region consisting of amino acid residues 123-419 of PCSK9 (the signal sequence also being left out of the numbering in Figure 26).

6.16 To the extent that the Claimants have argued that Figure 26 contains the “sole definition” of the catalytic

<sup>2</sup> Individual amino acids are often denoted by three letter codes (such as “Gln” for Glutamine, “Ser” for serine) and their position in a sequence (e.g. “Gln152”). Amino acids can also be denoted by a one

letter code. For instance “V” stand for valine, F for “phenylalanine” etc.



domain, it follows from the above that this is not the case. The meaning of “catalytic domain” follows from the interpretation given by the skilled person to the claim in accordance with the principles set out above. Moreover, the skilled person understands that the purpose of Figure 26 is not to define the catalytic (or other) domain of PCSK9 but rather to show a sequence comparison of the PCSK9 amino acid sequence and residues that were mutated in PCSK9 variants to examine the epitopes of the various antibodies (par. [0058] of the Patent). This does not take away that the skilled person recognises that the part of PCSK9 shown as the catalytic domain in Figure 26 is consistent in its meaning throughout the Patent description.

6.17 Feature F.3 additionally requires that the antibody “binds to the catalytic domain”. The skilled person will interpret this term in accordance with its ordinary, technically sensible meaning, i.e. the antibody must bind to at least one amino acid residue that lies within the catalytic domain. The claim leaves open where the binding (to the catalytic domain) must take place. The claim does not further specify what “binds to” means in qualitative nor in quantitative terms as long as the antibody “binds”.

6.18 The claim is not limited to antibodies that bind exclusively (or even predominantly) to amino acid residues that lie within (in other words to antibodies that bind to an epitope that lies within) the catalytic domain. Antibodies that bind to the catalytic domain and also to the other (i.e. the pro or V-) domains of PCSK9 fulfil feature F.3.

6.19 The description of the Patent does not lead to a different (narrower) interpretation of feature F.3. Par [0036] mentions an antibody that “binds to an epitope within residues 31-447 of SEQ ID NO: 3.” However, in the same paragraph, it is said that in some instances the antibody “binds to the catalytic domain”. The description also mentions other antibodies that bind to PCSK9 within a certain distance of particular amino acid residues (see e.g. par. [0037]). In addition, paragraphs [0400]-[0404] (Example 28) describe that the EGFa domain of LDLR binds to the catalytic domain of PCSK9. A crystal structure of PCSK9 bound to EGFa is shown and specific PCSK9 core interaction residues were defined. However, with regard to the binding site or location, the claim is not limited to the region where, according to the Patent’s findings, binding between PCSK9 and LDLR actually takes place. Rather, the claim is formulated more broadly and specifies a larger region, the catalytic domain, as the region to which binding must take place.

6.20 A technical functional reason why the antibodies must bind to the catalytic domain is not provided by the Patent. It is clear from the description that the requirement of binding of the antibody to the catalytic domain of PCSK9 is unrelated to any (auto)catalytic function of PCSK9. There is furthermore no apparent causal technical connection between binding to the catalytic domain and the function of the antibody. Such a technical connection is also not explained by the section of the Patent description that discusses

exemplary epitopes (par. [0235]-[0256] of the description). To the contrary, par. [0238] states that “In some cases, antigen binding proteins disclosed herein bind specifically to N-terminal prodomain, a subtilisin like catalytic domain and/or a C-terminal domain”. No reason is given for the requirement of binding to the (subtilisin like) catalytic domain.

6.21 The skilled person furthermore derives from the description that while the binding site of PCSK9 and LDLR is located within the catalytic domain, the binding of PCSK9 and LDLR involves only particular amino acid residues that are part of a smaller area within the catalytic domain. This confirms that the LDLR binding site on PCSK9 and the catalytic domain of PCSK9 are not congruent. The catalytic domain is (significantly) larger than the part of PCSK9 that interacts with the (EGFa domain on) LDLR. The description indeed points out in par. [0420] that: “it is clear that antigen binding proteins that bind to PCSK9 can also inhibit the interaction between PCSK9 and the LDLR by clashing with various regions of the LDLR (not just the site at which LDLR and PCSK9 interact)...” and in some instances an antibody “binds to PCSK9 at a position that is further away from [a location that overlaps with the interaction locations between PCSK9 and EGFa, Ab 31H4, and/or Ab 21B12]” and “can still be an effective neutralizing antigen binding molecule.” (par. [0423]).

6.22 That it is not excluded that the antibodies (or fragments) claimed besides binding to the catalytic domain, additionally bind to a region outside the catalytic domain such as the pro-domain or the V-domain, is furthermore consistent with the description and the position of both parties, as exemplified by antibody 31H4 which, undisputedly, is an embodiment falling within the scope of the claims of the Patent, and which binds to the catalytic domain of PCSK9, but also makes contact with amino acid residues from the prodomain (see Example 29).

6.23 However, feature F.3 should not be considered in isolation. Rather, its meaning must be determined in light of the claim as a whole and the underlying problem. In particular, features F.4 (and F.2) must also be considered. The skilled person recognises that the binding of the antibody required in F.3 is intended to have a **consequence**. Namely that which is mentioned in F.4: the antibody is intended to **prevent or reduce the binding of PCSK9 to LDLR**.

6.24 In the description it is explained that the antigen binding proteins can interfere with, block, reduce or modulate the interaction between PCSK9 and LDLR (par. [0421], [0426] of the Patent) and that the antigen binding proteins can bind to the catalytic domain in a manner such that PCSK9 cannot bind or bind as efficiently to LDLR (par. [0147], [0149] of the Patent). The binding according to feature 3 must therefore allow for this result to occur.

6.25 That it would be necessary for the binding to take place exclusively or primarily within the catalytic domain in order to fulfil this technical function is neither submitted by the parties nor otherwise apparent. To the contrary, as already discussed, antibody 31H4 binds to

the catalytic domain of PCSK9, but also makes contact with amino acid residues from the pro-domain (see Example 29). The skilled person will therefore understand any binding which also takes place in the catalytic domain and which fulfils this technical purpose - preventing or reducing the binding of PCSK9 to LDLR - to suffice. In fact, the description also points out in par. [0424] of the Patent: *“As will be appreciated by one of skill in the art, when the antigen binding molecules are large enough, such as a full antibody, the antigen binding molecule need not directly bind to the EGFA binding site in order to interfere with the binding of EGFA to PCSK9.”*

6.26 Consequently, the skilled person interprets the claims of the Patent as not being limited to antibodies that bind solely to amino acid residues within the catalytic domain, let alone to those amino acid residues (within the catalytic domain) that are directly involved in the interaction between PCSK9 and the EGFA domain of the LDLR. The skilled person will also bear in mind that the claims are not limited to any particular degree of reduction of the binding of PCSK9 to LDLR (as long as the antibodies are still suitable for the claimed medical use, see below feature F.2). Par. [0130] covers a very wide range of reducing percentages: *“...reduces the quantity of binding partner bound to the ligand by at least about 1-20, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, 80-85%, 85-90%, 90-95%, 95-97%, 97-98%, 98-99% or more (as measured in an in vitro competitive binding assay).”*

6.27 The “medical use features” F2.1 and F2.2 specify that the antibodies are for use in treating or preventing hypercholesterolemia or an atherosclerotic disease related to elevated serum cholesterol levels. Alternatively, the antibodies are for use in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels.

6.28 The Defendant has argued that the skilled person would understand that, even though acknowledging that no complete cure is required, the claims are limited to *“therapeutically meaningful”* treatments (e.g. par. 48 SoDCC). Claimants on the other hand say that *“any lowering of an elevated cholesterol level fulfils the characteristics of the treatment of hypercholesterolaemia”* (CC, 124)

6.29 As mentioned above, F2.1 and F2.2 require that the antibody used must be objectively suitable for the claimed use(s). As such, the antibodies must be able to be used for the treatment, prevention or reduction specified in the claim. However, this does not say anything about the “degree of effectiveness”. What is meant by the general terms “treating”, “preventing” or “reducing the risk”, in particular the degree to which this should be achieved, is not specified in the claim. The description gives a broad interpretation of treatment of hypercholesterolemia (see e.g. Example 20, *“reduced serum cholesterol levels in comparison to arthritis patients not receiving the treatment prevention”*), as well as of the term “prevention” see e.g. par. [0144] of the Patent: *“...the likelihood of the occurrence of the event*

*has been reduced in the presence of the compound or method.”*

6.30 In view of the teaching of the Patent as a whole, the skilled person would understand the claimed treatment not to be limited to a particular lowering of cholesterol levels as long as there is some (measurable) reduction of cholesterol levels in vivo and provided the therapy is safe. The Central Division furthermore notes that the claimed use encompasses the administration of the claimed antibodies together with at least one other cholesterol-lowering agent, notably statins (claims 6 and 7 of the Patent). This confirms the understanding of the skilled person that also a (very) small cholesterol-lowering effect caused by the claimed antibodies can be “therapeutically effective” in the sense of the claimed treatments.

6.31 Based on the above interpretation, which combines an adequate protection for the patent proprietor with sufficient legal certainty for third parties, the Central Division accepts the position of the Defendant that not all antibodies that may conceivably bind to the catalytic domain are covered by the claim. By the same token, the skilled person will understand that antibodies that do not bind to the catalytic domain (but exclusively to the pro- or V-domain) are not covered by the claims. Thus, F.3, F.4 and F.2 indeed limit the number of antibodies falling under the claim. On the other hand, the claims are not limited to antibodies which, like “reference antibodies” 21B12 and 31H4, are able to directly or sterically block PCSK9 from binding to LDLR by binding to or near residues that overlap with the EGFA binding region of PCSK9 (as suggested by Defendant, see e.g. 34 DtCC, also see above). For the skilled person, it will appear that the patentee has chosen the present broader claim wording instead of defining the claimed antibodies in a narrower way.

## 7 Priority and novelty of the Main Request

7.1 The Claimants challenged the validity of the priority claimed by the Patent. In particular, the Claimants are of the view that the claims of the Patent cannot be accorded an earlier priority date than 4 August 2008 (the filing date of P4). The Central Division does not follow the Claimants and finds that the Patent can successfully claim priority from P3.

7.2 In support of their case, Claimants argued that the Patent contains its own definition of the catalytic domain, which can be found in Figure 26, based on which the catalytic domain comprises amino acids 123-419 of PCSK9 (following the numbering of SEQ ID NO: 1). Figure 26 is not included in the priority documents P1 to P3 but was introduced only in P4. The definition of the catalytic domain in the Patent from Figure 26 as comprising amino acids 123-419 can therefore, still according to the Claimants, not be derived directly and unambiguously from priority documents P1 to P3. The introduction of Figure 26 in P4 resulted in a different definition of the term “catalytic domain” in P4. In P1-P3 the catalytic domain could be any prior art definition (with different definitions of the catalytic domain being used and therefore derivable for the skilled person from different prior art documents).

7.3 The Claimants essentially argue that the invention in P3 is not the “same invention” as in P4 and as claimed in the Patent and that therefore the priority right is not valid, at least in relation to P3.

7.4 Defendant argues that the Patent is entitled to priority from at least P3 which was filed on 9 January 2008. Defendant says that in view of P3, the skilled person would have understood that the catalytic domain of PCSK9 means amino acids 153-449 of the full-length sequence, corresponding to amino acids 123-419 of SEQ ID NO: 1. The definition of the catalytic domain has not changed between P3 and P4. Figure 26 is not a new definition of the catalytic domain and is consistent with the meaning of catalytic domain in P3.

#### **Legal framework**

7.5 In accordance with [Article 87 EPC](#) any person who has duly filed an application for a patent, a utility model or a utility certificate, or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application. This right can be claimed in accordance with [Article 88 EPC](#). The effect of a right of priority is that the priority date counts as the filing date of the European patent application for determining the state of the art ([Article 89](#) in connection with [54\(2\) and \(3\) EPC](#)).

7.6 The Central Division interprets the requirement of “the same invention” in [Article 87 EPC](#) such that a claimed invention is to be considered the same invention as the invention in a previous application if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole (cf. [EPO Enlarged Board of Appeal 31 May 2001, G2/98, ECLI:EP:BA:2001:G000298.20010531](#)).

#### **Priority in the present case**

7.7 Applying the above legal standard to the case at hand, the Central Division is of the opinion that the invention claimed in the Patent is disclosed in previous application P3 and that the Patent therefore validly claims priority of P3.

7.8 The skilled person derives from P3 that PCSK9 is a prohormone-proprotein convertase in the subtilisin (S8) family of serine proteases containing a prodomain, catalytic domain, and V-domain (or C-terminal domain) (e.g. par. [0003], [0004] P3). This is not disputed by the Claimants. From par. [0004], [0005], [0031]-[0032] in combination with Figs. 1A-1B in P3, the skilled person derives that the pro-domain means amino acids 31-152. A signal sequence is formed by amino acids 1-30 and is followed by the three domains. This is still not in dispute. Example 27, which describes a method for determining where various antibodies bind to PCSK9 (par. [0418]-[0419] in P3), discloses that the ProCat domain means amino acid residues 31-449 and V-domain means amino acid residues 450-692. This teaching is confirmed in par. [0431] of Example 30 (which shows that antibody 21B12 binds to the catalytic domain of PCSK9), par. [0453] of Example 34 and par. [0456] of Example 35 which all refer to residue 449 as

the last residue of the catalytic domain. Example 33 in par. [0448] of P3 also mentions a PCSK9 ProCat together with a V-domain (450-692) sample. From this information, the skilled person will derive (directly and unambiguously) that the catalytic domain spans amino acids 153-449 (and that the V-domain starts at amino acid 450), corresponding to amino acids 123-419 in the numbering of SEQ ID NO: 1 without the signal sequence.

7.9 The fact that P3 in Example 33 also mentions a PCSK9 ProCat protein/variant consisting of amino acids 31-454 does not lead the skilled person to conclude that there is no (or at best an ambiguous) definition of the catalytic domain of PCSK9 in P3. This construct was generated for expression in baculovirus infected insect cells and subsequent purification, and was a construct that did not have a V-domain. In the case of the construct “PCSK9 449TEV”, a TEV protease cleavage site was, as brought forward by Defendant (44 SoD) and not (specifically) contested by Claimants, deliberately inserted between PCSK9 residues 449 and 450 to generate PCSK9 ProCat (31-449) and Vdomain samples. This confirms the skilled person’s understanding of the ProCat (and thereby also the “Cat”) domain ending at amino acid 449 (corresponding to residue 419 without the signal sequence).

7.10 The meaning of “catalytic domain” as follows from P3 corresponds to how the skilled person interprets said term in the claims of the Patent as granted (see above, 6.12 et seq.).

7.11 Figure 26, which indeed has been added in P4 and which is also included in the Patent, is consistent with the above interpretation but does not contain any new information with respect to the amino acid sequence of the catalytic domain of PCSK9. Contrary to what the Claimants have argued, as also follows from the discussion under claim interpretation above, the skilled person does not see Figure 26 as the (sole) definition of the catalytic domain in P4 or the Patent. Rather Figure 26, whilst keeping consistent with the understanding of the pro-, catalytic and V-domains as follows from P3, shows a sequence comparison of the PCSK9 amino acid sequence (“PCSK9parent”) and residues that were mutated in certain PCSK9 variants (“PCSK9mutants”). With respect to the definition of PCSK9’s catalytic domain, Figure 26 therefore does not add or change any technical information vis-à-vis the disclosure of P3 nor does it comprise the sole definition of “catalytic domain” in the Patent (see above, 6.16 which reasoning applies mutatis mutandis here).

7.12 The mere fact that various prior art documents contain different definitions of which amino acid residues make up the catalytic domain of PCSK9, as pointed out by the Claimant, does not affect the skilled person’s understanding of the priority documents and the Patent. To the contrary, absent the existence of a commonly accepted state of the art definition of the catalytic domain of PCSK9 (the existence of which has not been brought forward by any of the parties), the skilled person will derive the meaning of “catalytic



domain” first and foremost from the priority and Patent documents themselves.

7.13 In conclusion, as the claimed subject matter is disclosed in P3, the arguments of the Claimants fail and the Patent can successfully claim priority from (at least) P3. Accordingly, the relevant date for assessing the contents of the prior art that will be used by the Central Division is **9 January 2008**.

#### **Novelty**

7.14 The Claimants have argued that the Patent lacks novelty under [Article 54\(3\) EPC](#) over two documents (C1 and C2) the (earliest) priority dates of which are 7 February 2008. As it follows from the above that the Patent validly claims an earlier priority date of at least P3, documents C1 and C2 are not part of the state of the art under [Article 54\(3\) EPC](#) and therefore cannot be novelty destroying.

#### **8 Inventive step of the Main Request**

8.1 In the present case, the Central Division comes to the conclusion that the claimed subject matter is obvious and does not involve an inventive step.

##### **Legal framework inventive step**

8.2 According to [Article 56 EPC](#), an invention shall be considered as involving an inventive step if, having regard to the state of the art, it is **not obvious to a person skilled in the art**.

8.3 Whether inventive step is acknowledged is always to be assessed in each individual case and requires a legal evaluation of all relevant facts and circumstances. As held by the [Court of Appeal in NanoString/10x Genomics](#) (p. 30, fourth par.) the burden of presentation and proof with regard to the facts from which the lack of validity of the patent is derived and other circumstances favourable to the invalidity or revocation lies with the claimant in a revocation action ([Art. 54](#) and [65\(1\) UPCA](#), [Rules 44\(e\)-\(g\)](#), [25.1\(b\)-\(d\) RoP](#)). Even though proof of certain facts, if contested, may thus be required, the ultimate assessment of the relevant facts circumstances is a question of law which does not lend itself to the taking of evidence.

8.4 An **objective approach** must be taken to the assessment of inventive step. The subjective ideas of the applicant or inventor are irrelevant. In principle, it is also irrelevant whether the invention is the result of serendipity or of systematic work involving (potentially costly and laborious) experimentation. It is only relevant what the claimed invention actually contributes to the prior art.

8.5 Inventive step is to be assessed from the point of view of the **skilled person** on the basis of the **state of the art** as a whole including the skilled person’s common general knowledge. The skilled person is assumed to have had access to the entire publicly available art on the relevant date. The decisive factor is whether the claimed subject matter follows from the prior art in such a way that the skilled person would have found it on the basis of their knowledge and skills, for example by obvious modifications of what was already known.

8.6 In order to assess whether or not a claimed invention was obvious to a skilled person, it is first necessary to

determine a starting point in the state of the art. There has to be a justification as to why the skilled person would consider a particular part of the state of the art as **a realistic starting point**. A starting point is realistic if its teaching would have been **of interest** to a skilled person who, at the priority date of the patent at issue, was seeking to develop a similar product or method to that disclosed in the prior art which thus has a similar **underlying problem** as the claimed invention (cf. [Court of Appeal Nanostring/10x Genomics](#), p. 34 under “cc” in the German original version, “Für eine Fachperson, die sich zum Prioritätszeitpunkt des Verfügungspatents vor die Aufgabe gestellt sah war [...] D6 von Interesse”). There can be several realistic starting points. It is not necessary to identify the “most promising” starting point.

8.7 Comparing the claimed subject matter, after interpretation following the guidelines provided above under “claim interpretation”, and the prior art, the subsequent question is whether it would be **obvious** for the skilled person to, starting from a realistic prior art disclosure, in view of the underlying problem, arrive at the claimed solution. If it was not obvious to arrive there, the claimed subject matter meets the requirements of [Article 56 EPC](#).

8.8 In general, a claimed solution is obvious if, starting from the prior art, the skilled person would be **motivated** (i.e. have an incentive or in German: “*Veranlassung*”, see the [CoA in NanoString/10x Genomics](#), p. 34) to consider the claimed solution and to implement it as a **next step** (“*nächster Schritt*”, [CoA in NanoString/10x Genomics](#), p. 35, second par.) in developing the prior art. On the other hand, it may be relevant whether the skilled person would have expected any particular difficulties in taking any next step(s). Depending on the facts and circumstances of the case, it may be allowed to combine prior art disclosures.

8.9 A **technical effect** or advantage achieved by the claimed subject matter compared to the prior art may be an indication for inventive step. A feature that is selected in an **arbitrary** way out of several possibilities cannot generally contribute to inventive step.

8.10 The Central Division emphasises that hindsight needs to be avoided. The question of inventive step should not be answered by searching retrospectively, with knowledge of the patented subject matter or solution, for any (combination) prior art disclosures from which that solution could be deduced.

##### **Lagace (C3)**

8.11 Claimants have taken the position that [Lagace et al. 2006](#) (“Lagace”, C3) should be used as a starting point for the assessment of inventive step. Defendant in the DtR took the position that [Graham 2007](#) (D19, “Graham”), being the first scientific publication to provide in vivo data describing a therapeutic modality that targets PCSK9 (with antisense oligonucleotides, or ‘ASOs’), was a “closer” and “more realistic” starting point (113 DtR). Graham was considered the “closest prior art” by the EPO Examiner in charge of the examination of the Patent. In its Case Summary, Defendant advocated a “holistic approach” to inventive

step which avoids being fixated on one specific passage in one specific document. The broader context of the state of the art is relevant, and focussing on a single embodiment or document leads to tunnel vision based on hindsight according to the Defendant.

8.12 It follows from the above that it is actually not in dispute between the parties that Lagace at least is a realistic starting point for the assessment of inventive step. This is also the view of the Central Division.

8.13 Lagace has as its title “*Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice*”. In the introduction, Lagace discusses the background knowledge on PCSK9 and its biological role, see p. 2995, rh col., second par.:

“*The biological activity of PCSK9 was revealed through overexpression studies in mice. Overexpression of PCSK9 posttranscriptionally reduced the amount of LDLR protein in liver (3, 8–10). 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 (11). These conclusions were supported by studies in 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(12). 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 (13)*” (underline CD)

8.14 Next in the introductory part, Lagace goes on to discuss what the focus of the research project reported in the article is:

“*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. The mechanism by which PCSK9 reduces the number of LDLRs is still undetermined. For example, it is unclear whether PCSK9 acts to destroy LDLRs in the secretory pathway or whether it acts outside of the cell. In the current studies, we provide evidence that extracellular PCSK9 can be internalized by cultured liver cells and fibroblasts in a manner that is largely dependent on LDLRs. Incubation with extracellular PCSK9 led to loss of LDLRs.*” (underline CD)

8.15 Based on the experimental data as reported in Lagace, the authors conclude “*that secreted PCSK9 associates with the LDLR and reduces hepatic LDLR*

*protein levels*” (Abstract, last sentence). In the final par. of the “Discussion section”, the authors note that:

“*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. Inasmuch as overexpression of the catalytically inactive form of PCSK9 in mice did not alter LDLR protein levels (9), an inhibitor of PCSK9’s protease activity in the ER should be sufficient to block its ability to reduce LDLR protein levels. 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.*” (underline CD)

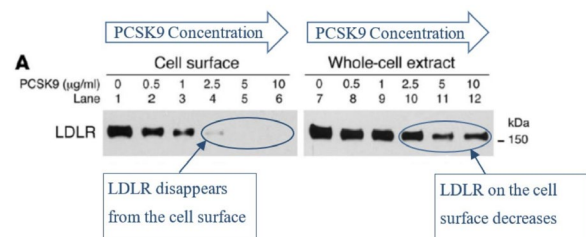
8.16 Lagace discloses a number of *in vitro* and *in vivo* experiments in support of the conclusions reached therein.

8.17 Further to a previous report showing that PCSK9 could be detected in human plasma by immunoprecipitation (reference 15, Zhao et al., C42), levels of PCSK9 in plasma were measured in 72 volunteers. It was found that the plasma levels ranged from approximately 50 to approximately 600 ng/ml. Lagace states:

“*These measurements demonstrate that considerable amounts of PCSK9 circulate in plasma and provided a range of physiologically relevant PCSK9 concentrations*” (Lagace, p. 2996, lh col. second par.)

8.18 To test the possibility that PCSK9 acts on LDLRs after secretion from the cell, Lagace et al. assessed the rate and extent of secretion of PCSK9 from cultured human hepatoma HepG2 cells. The authors conclude that “*PCSK9 is rapidly and efficiently secreted from these cells*” (Lagace, p. 2996, lh. col. first par.).

8.19 In a next experiment, it was determined whether the secreted form of PCSK9 can reduce the number of LDLRs when added to cultured HepG2 cells. The results are reported in Figure 2 of Lagace. It was observed that the number of cell surface LDLRs declined after incubation with PCSK9 in a concentration dependent manner. Incubation with PCSK9 also decreased whole-cell LDLR levels. This is shown in the below Figure 2A (top part, annotated by Claimants, 169 CC, not (specifically) contested by Defendant):



8.20 The authors then report that a known mutant form of PCSK9 (D374Y)<sup>3</sup>, which had been shown previously to be associated with severe hypercholesterolemia, was taken up by cells approximately 10-fold more efficiently than the wild-type protein (Lagace, p. 2997, lh. col. first par.)

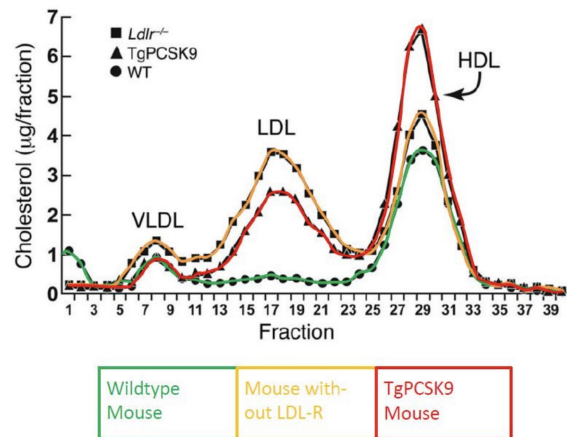
8.21 In a further experiment, the authors determined whether the cellular association or uptake of PCSK9 was dependent on LDLRs. For this purpose, cells were used that came either from mice that produce LDLR normally (“wild-type” mice) or from mice that do not produce LDLR because of a gene knockout (“*Ldlr*<sup>-/-</sup>” mice). The results are shown in Figure 4A of Lagace which shows that the PCSK9 uptake in wild-type cells was high and was markedly reduced in the *Ldlr*<sup>-/-</sup> mice that did not produce LDLR. In Figure 4B and 4C it is shown by immunofluorescence staining of the cells that LDL-R and PCSK9 co-localize intracellularly in endocytic vesicles after uptake. According to the authors “*Considered together, the data ... suggest that PCSK9 and LDL-R are taken up together into the cell and travel together to endosomes/lysosomes*” (Lagace, p. 2997, lh. col. last par.-p.2998 right col. first par.), which is a compartment in the cell that degrades proteins and explains the reduction in LDLR (175 CC, not disputed by the Defendant). Another experiment showed that PCSK9 still associated with cells in the absence of ARH (a protein that was known to be involved in LDLR internalisation, E2, par. 14). The experiment showed that “*internalization is required for PCSK9 to reduce the cell-surface expression of LDLR protein*” (Lagace, p. 2999, rh. col. first par.)

8.22 In another set of experiments, the authors test the possibility that the mutant form of PCSK9, PCSK9(D374Y), binds stronger to the LDLR. Figure 5D shows that both purified wildtype PCSK9 and the D374Y mutant bind to the extracellular domain of the LDLR protein in a concentration-dependent manner. The mutant appeared to bind with a greater affinity (Lagace, p. 2998, rh. col. second par.). According to Lagace, also taking into account the experiments shown in Figure 5, “[c]ombined this indicates that PCSK9(D374Y) binds to LDLRs with higher affinity than does wild-type PCSK9, a finding that correlates with the enhanced ability of the mutant PCSK9 to destroy LDLRs.” (Lagace, p. 2998, rh. col. last sentence).

8.23 Lagace also carried out in vivo experiments in mice that were genetically modified to express human PCSK9 in the liver (called “TgPCSK9 mice”). The authors report:

“As shown in Figure 7A, transgenic overexpression of human PCSK9 eliminated LDLR protein expression in liver and caused a marked increase in plasma LDL cholesterol levels (Figure 7B). The increase in plasma LDL cholesterol was similar to that measured in *Ldlr*<sup>-/-</sup> mice that lacked LDLRs in all tissues.”

8.24 Figure 7B (annotations by Claimant, 180 CC) is reproduced below.



8.25 Lagace et al. also investigated whether PCSK9 secreted from TgPCSK9 mice that over-express PCSK9 could lower the LDLR level in a wildtype (WT) mouse by connecting the blood circulation of the WT mice to that of the transgenic mice (creating what is called in the article “parabiosed” mice). Lagace reports: “*The LDL-R protein was essentially undetectable in livers of wild-type mice after they were parabiosed with TgPCSK9 mice (Figure 8C) indicating that PCSK9 was active in mouse plasma*” (Lagace, p. 3000, rh. col. last sentence – p. 3001, first par. first sentence).

8.26 The Central Division finds that from the teaching of Lagace as a whole, and in particular the passages cited above, the skilled person at the relevant date, January 2008, would have realised that Lagace was interested in finding out more about the mechanism by which PCSK9 reduces the number of LDLRs. The reason for this interest, as indicated in the article itself, was the background knowledge that loss of PCSK9 expression resulted in lower plasma cholesterol levels in vivo. Accordingly, neutralisation of the activity of (secreted) PCSK9 is mentioned as a potential approach for the treatment of hypercholesterolemia.

8.27 This makes Lagace a realistic starting point for the assessment of inventive step of the claimed subject matter, the underlying problem of which is to provide a treatment for hypercholesterolemia (or other conditions related to elevated serum cholesterol levels) using PCSK9 as a target. The Defendant has not brought forward any concrete arguments as to why Lagace would not be a realistic starting point. It does not follow from the assertion that Graham is “more realistic” or “closer” that Lagace is not a realistic starting point. Defendant’s arguments as to the speculative nature of the teaching of Lagace are to be discussed in the context of obviousness, but do not support the conclusion that the skilled person would not have been interested in Lagace at the relevant date.

8.28 From the above it follows that a skilled person who was interested in developing a treatment for

<sup>3</sup> D374Y stands for a substitution of the amino acid aspartic acid (D) for the amino acid tyrosine (Y) at position 374 in the amino acid sequence of PCSK9.



hypercholesterolemia targeting PCSK9 would, according to Central Division without doubt, have been interested in Lagace. Having concluded that Lagace is a realistic starting point, the Central Division does not have to examine in detail whether another starting point, in particular Graham as suggested by the Defendant, is “more promising”. As set out above, the claimed subject matter has to be inventive over any realistic starting point.

8.29 Based on the experiments reported in the paper, Lagace et al conclude the Discussion section with the statement as already depicted above and repeated here for completeness:

*“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.” (underline CD)*

8.30 It follows from the above that Lagace discloses that the development of anti PCSK9 antibodies that block the LDLR:PCSK9 interaction can be explored for the treatment of hypercholesterolemia. Lagace does not disclose any antibodies that bind to the catalytic domain of PCSK9 and block the interaction between PCSK9 and LDLR which are actually used for the treatment of hypercholesterolemia. Absent such a disclosure, these differences must be taken into account when assessing obviousness.

#### **Obviousness**

8.31 The Central Division finds that the skilled person having the aim to, starting from Lagace, provide a treatment or way of prevention of hypercholesterolaemia or atherosclerotic disease associated with elevated serum cholesterol levels or for use in reducing the risk of recurrent cardiovascular events associated with elevated serum cholesterol levels targeting PCSK9 to regulate levels of LDLRs (and thereby LDL), would as a next step have pursued the route of developing antibodies that block the interaction between PCSK9 and LDLR as explicitly suggested by Lagace. Pursuing that route the skilled person would have ended up with antibodies as defined in the claims without inventive skill.

#### **PCSK9 was a genetically validated target for lowering LDL levels in the blood**

8.32 At the hearing, the Defendant disputed that at the relevant date PCSK9 was considered as a (genetically) “validated” target for the treatment of hypercholesterolemia. Defendant argued that there was “a possibility that PCSK9 might be a therapeutic target.” In its Case Summary (par. 2), Defendant refers to PCSK9 as a “potentially interesting therapeutic target”. The Defendant furthermore brought forward that PCSK9 antibodies were the first antibody treatment in the cardiovascular area of medicine.

8.33 According to the Central Division, even though there was no approved therapy at the relevant date targeting PCSK9 and the target may not have been a “validated therapy” in that sense, the relevance of and

significant (commercial) interest in PCSK9 as a target for the treatment of hypercholesterolemia had been well established and was generally accepted at the relevant date, in particular on the basis of the then available genetic data. This is confirmed in Lagace itself (see above, e.g. introduction and last paragraph of the Discussion) and is moreover corroborated by the fact that at the relevant date a considerable number of pharmaceutical companies were pursuing various (according to Defendant “essentially all”, cf. oral hearing slide 27) options to target (inhibit) PCSK9. One of these companies was BMS, where Defendant’s expert Dr. [...] was employed, who declares: “As I explain above, the discovery of the gene encoding PCSK9 was made in 2003. The association of PCSK9 with hypercholesterolemia was a significant breakthrough. The possibility of reducing the prevalence of hypercholesterolemia and its established connection with ASCVD [atherosclerotic cardiovascular disease, CD] meant that there was significant value in targeting PCSK9.” (E5, par. 203). This is also confirmed in the joint expert report of Dr. [...] and Prof. [...] prepared for Australian proceedings between the parties: “We agree that the human genetic validation was very strong, and it was clearly desirable to seek a PCSK9 inhibitor to reduce LDL levels. The genetic validation of a drug target is rare and in this case was the reason multiple pharmaceutical companies had PCSK9 inhibition programs.” (D95, 2.2). It is not in dispute that the relationship between elevated cholesterol levels and atherosclerosis was commonly known at the relevant date (see Dr. [...] above, also 442 SoD).

8.34 There was accordingly a strong incentive at the relevant date for the skilled person to seek a PCSK9 inhibitor to reduce LDL levels in order to be able to treat hypercholesterolemia (and atherosclerotic diseases).

8.35 The skilled person faced with the task of finding a treatment for hypercholesterolemia targeting PCSK9 would according to Defendant not have pursued an antibody approach to targeting PCSK9, at least not with a reasonable expectation of success. Defendant gives the following reasons. First, the biological mechanism of PCSK9, in particular its site of action, were still unknown at the priority date. Second, it was not known which domains of PCSK9 interact with LDLR which would complicate an antibody approach. Besides these (fundamental) issues, there were further reasons why the skilled person would not have had a reasonable expectation of success for an antibody approach. Given all of these unknowns, the skilled person would rather follow an “agnostic approach”, such as ASOs (as Graham did in D19). Finally, the Defendant submits, even if the skilled person would have considered an antibody approach, they would not inevitably have ended up with antibodies that fall within the scope of the claim. These arguments do, however, not convince the Central Division.

#### **Lagace teaches the skilled person that PCSK9 functions extracellularly in vivo**

8.36 It is not in dispute between the parties that the skilled person at the relevant date would have realised

that antibodies can only be effectively used against extracellular targets. The central plank of the Defendant's non-obviousness case is that the skilled person would not consider that Lagace, or any other prior art reference, showed that PCSK9's extracellular mechanism was physiologically relevant and therefore would not pursue the development of therapeutic antibodies to inhibit PCSK9 (extracellularly), or at least would conclude that trying to develop therapeutic antibodies to inhibit PCSK9 had no reasonable expectation of success.

8.37 The skilled person who, as rightly pointed out by the Defendant, is not an academic wishing to explore and understand the PCSK9 mechanism, but is a team that is set out to solve a problem, will consider a prior art document in its entirety in light of their common general knowledge and make realistic and practical deductions from a prior art teaching. Lagace will be read as such by the skilled person.

8.38 Lagace reports:

*"considerable amounts of PCSK9 circulate in plasma and provided a range of physiologically relevant PCSK9 concentrations."* (C3 2996, rh. col., second par.)

*and on p. 3002, lh. col. last par. - 3002, rh. col. top:*

*"Considered together, the available data now suggest that PCSK9 can function both extra- and intracellularly, but we do not know which pathway predominates under normal and/or pathologic conditions. Currently, all studies suggesting that the protein functions intracellularly have been performed using PCSK9 overexpression via a strong CMV promoter. Overexpression may permit association of PCSK9 and the LDLR in an intracellular compartment that does not occur physiologically. In the current studies, we were able to demonstrate that physiologically relevant concentrations of PCSK9 could significantly reduce the number of cell-surface LDLRs"* (underline CD).

8.39 The above, according to the Central Division, is not a "tacit admission" (127 Dtr) that the authors did not know whether the extracellular pathway was "even relevant" at PCSK9 concentrations that occur in vivo, but rather a clear statement, supported by the experimental data reported in Lagace, that PCSK9 acts in any event extracellularly (at physiologically relevant concentrations). The possibility that an intracellular pathway predominates under pathological conditions is left unanswered by the authors, but with the remark that all studies suggesting that PCSK9 functions intracellularly have been performed under overexpression of PCSK9 via a strong CMV promoter. Overexpression may permit association of PCSK9 and the LDLR in an intracellular compartment. Rather (and by contrast), the authors emphasize their findings in relation to the extracellular function of PCSK9 at "physiologically relevant concentrations of PCSK9".

8.40 Against this background, Lagace draws the conclusion that "*secreted PCSK9 associates with the LDLR and reduces hepatic LDLR protein levels*" (Lagace, abstract, last sentence).

8.41 The Defendant refers to the expert report of Dr. [...] who states that "*There were many unanswered questions concerning the data in this paper that needed to be investigated before one could accept the concluding statements made by the authors.*" (E5, par. 98, 148 Dtr). In the view of the Central Division, however, the skilled person is aiming to solve a problem and in doing so is considering which next step(s), if any, are realistically to be taken. Absent any apparent errors or omissions in a prior art document, a skilled person will not be overly cautious (nor creative) and does not analyse every experiment in a prior art document in isolation with a view to the questions it does not answer but will rather be inclined to accept published (and peer reviewed) research results and reasonable conclusions drawn from those results at face value.

8.42 The most pertinent point raised in this respect is that according to the Defendant (again with reference to expert reports from Dr. [...]) the skilled person would realise that the data reported in Lagace are based on experiments that do not reflect physiological conditions in the body and use artificially high concentrations of PCSK9. In support, the Defendant refers to a paper by Prof. [...] commenting on the previous studies (by the same research group) in Lagace (see C11, p.73, lh. col., last sentence):

*"A potential artifact of the cell-culture studies, adenoviral studies in the liver and the parabiosis studies relates to the supraphysiological amounts of PCSK9 used to generate LDLR degradation. Overexpression might promote an interaction between PCSK9 and the LDLR in a cellular compartment that does not usually occur."* (quote in 137 Dtr, 36 Case Summary, underline CD).

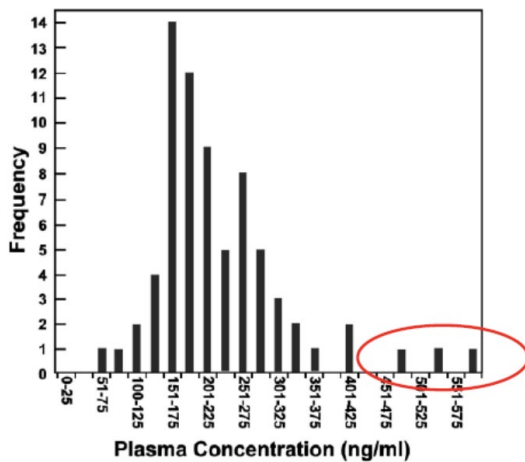
8.43 However, according to the Central Division, the skilled person will also take note of the second part of the paragraph, which reads:

*"To address this issue, the circulating levels of PCSK9 in human plasma were measured and found to range from ~50 to ~600 ng ml<sup>-1</sup>. The concentration of purified PCSK9 needed to promote LDLR degradation (~500 ng ml<sup>-1</sup>) falls within this range [23]."* (reference 23 is Lagace, underline added CD) (C11, p. 73 lh. col., last sentence, rh. col. first sentence, underline CD).

8.44 The last sentence of the paragraph thus informs the skilled person that the authors were aware of the potential artifact of artificially high PCSK9 amounts but that they performed an experiment to control for this issue. The Defendant criticises this control by referring to supplementary data from Lagace showing that only three out of 72 patients in fact had a PCSK9 plasma level of 500 ng/ml or higher (C3a, Supplemental Data to Lagace, the Defendant refers to these data points as "outliers"). Fig. 1 according to Defendant shows that the

median PCSK9 level was about 200 ng/ml, or around 2-3 nM, Figure taken from par. 138 Dtr, annotations by Defendant):

Suppl. Figure 1

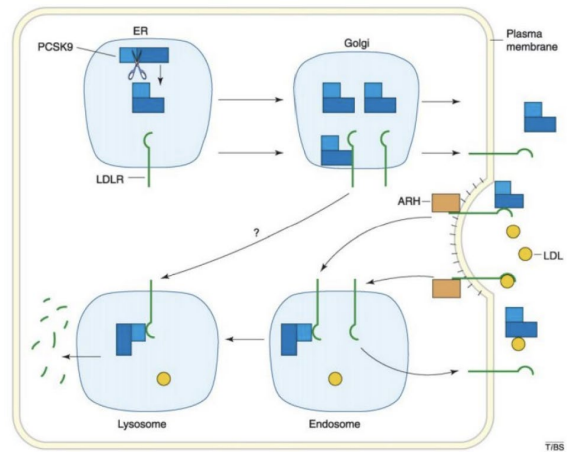


(C3a, Supplemental Figure 1)

8.45 The Defendant nor any of their experts – rightly in the view of the Central Division – dispute that Lagace shows that (secreted) PCSK9 is indeed present in human plasma in the range reported in Lagace. Nor does the Defendant argue that a plasma level of 500 ng/ml is as a matter of fact physiologically irrelevant. Rather, the Defendant argues that the skilled person would have realised that 500 ng ml ml-1 (the lowest concentration used to demonstrate the extracellular effect of PCSK9 in the experiments reported in Lagace) is such that the skilled person would not have found the control “persuasive” (138 Dtr). Indeed, 500 ng ml ml-1 is at the high end of the PCSK9 range reported in plasma of subjects (~50 to ~600 ng ml-1 ). The Central Division does, however, not follow the Defendant in that this would for the skilled person discredit the teaching of Lagace, in particular the conclusions reached therein as to the biologically (in vivo) relevant mechanism of action of PCSK9, in the context of all the experiments and data reported in the paper as a whole, i.e. that PCSK9 is active as a secreted protein in a physiologically relevant way.

8.46 Further support for the acceptance by the skilled person of the existence of PCSK9’s extracellular pathway and the physiological relevance of the extracellular pathway is found in several other prior art references published after Lagace.

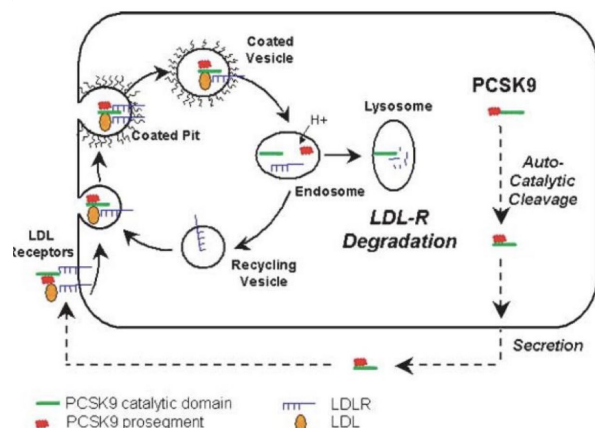
8.47 First of all, there is the review article by [redacted] et al. (C11), which was already mentioned above. Figure 2 confirms that, despite leaving open the possibility of the existence of an intracellular pathway (denoted with a question mark) and despite uncertainties at which specific sites in the cell PCSK9 functions, the secretion of PCSK9 and interaction with LDLR at the cell surface were 37 accepted (there is no question mark in Figure 2 at the extracellular pathway, depicted on the right):



8.48 The acceptance of the extracellular pathway is furthermore confirmed in Qian et al. (C6). This article was published by a research team from the pharmaceutical company Eli Lilly. In early 2007, they report:

“...we have demonstrated that 1) secreted recombinant PCSK9 is fully functional in reducing LDLR protein levels both in cultured cells and in vivo; 2) PCSK9 undergoes LDLR-mediated endocytosis; and 3) PCSK9 binding to LDLR is critical for PCSK9 function.” (C6, p. 1494, rh. col. second par.).

This conclusion is based on the authors’ own research, including in vivo mice experiments (see Figure 3, concluding in the caption to Figure 3 that “PCSK9 recombinant protein reduces hepatic LDLR and increases plasma LDL cholesterol in vivo.”) and including an in vitro experiment showing that disrupting PCSK9 binding to the cell surface LDLR extracellular domain was sufficient to markedly attenuate PCSK9 function (Fig. 6 and p. 1497, lh. col. first par.). Qian et al. also refer back to the Lagace paper (reference 20 in Qian et al.). Based on these findings, Qian et al. provide a “working model” in Figure 7 showing the role of PCSK9 acting (exclusively) as a secreted (extracellular) protein that interacts with LDLR.



8.49 The publications relied on by the Defendant, even if the Central Division were to accept in favour of the Defendant that, although most of these do not form part of the state of the art, their contents are representative of what was (not) known at the priority date about PCSK9’s mechanism of action, would not have raised



substantial doubts in the mind of the skilled person on the existence of the extracellular pathway. At most these publications raise questions concerning the relative contribution of the extracellular pathway and a possible intracellular pathway. Lopez 2008 (C14), for example, states “*[a]nother open question is whether PCSK9 acts primary [sic] as an intracellular or a secreted factor.*” (p. 189, lh. col. under “Conclusion”). Grefhorst 2008 (D23, p. 1303) states: “*[c]urrently, the relative contribution of the intracellular pathway versus the exogenous pathway of PCSK9-mediated LDLR degradation is not known.*” (underline Central Division). Thus, none of these references calls into question the existence of the extracellular pathway as such. This is also true for McNutt (D25, published in 2009) which, despite the citation from the Abstract highlighted by the Defendant in par. 108 DtCC, indeed also seems to presuppose the existence and relevance of an extracellular pathway, e.g. see the further quote by Defendant in par. 199 DtCC: “*address an unresolved issue in PCSK9 biology, whether PCSK9 functions primarily intracellularly to degrade LDLRs or as a secreted protein that acts on LDLRs at the cell surface.*” (underline CD.). Poirier (D26) likewise focussed on the “*relative contribution of the intra- versus extracellular pathway*” (see citation 202 DtCC, underline CD). In fact, Poirier confirms that even if there was uncertainty in relation to the relative contribution of the intra- versus the extracellular pathway, this would not affect the viability of an approach directed towards the extracellular pathway for the treatment of hypercholesterolemia, see D26, Abstract, last sentence: “*Therefore, targeting either pathway, or both, would be an effective method to reduce PCSK9 activity in the treatment of hypercholesterolemia and coronary heart disease.*” (underline CD).

8.50 Weighing the evidence before the Central Division, it cannot be concluded that the skilled person at the relevant date would have serious doubts about whether PCSK9 indeed acts (at least also) extracellularly in vivo as taught by Lagace, at least not doubts that were of such a nature that these would have dissuaded the skilled person from pursuing an antibody approach to block the interaction between PCSK9 and LDLR as suggested by Lagace. In fact, in a contemporaneous patent application from [...] on which Dr. [...] is mentioned as one of the inventors, it is stated: “*The secreted form of PCSK9 appears to be the physiologically-active species*” (C37, par. [0006]).

8.51 In line with this conclusion and providing additional corroboration, Lagace was not the only prior art disclosure that provided a concrete incentive to develop antibodies against PCSK9 to inhibit PCSK9/LDLR interaction to the skilled person.

8.52 Horton et al. conclude in their 2007 review paper discussed above:

*“The low plasma LDL-C levels associated with loss-of-function mutations in PCSK9 indicate that inhibition of PCSK9 either through small molecules, antibodies or RNAi should be effective cholesterol-lowering drugs*

*independently of statins.” (C11, p. 75, lh col. second par., last sentence).*

8.53 Cunningham et al., who resolved the crystal structure of PCSK9 and published their findings in May 2007, conclude their report as follows:

*“Genetic evidence suggests that PCSK9 is an attractive target for the treatment of cardiovascular disease. In theory, PCSK9 could be targeted by a cell-permeable protease inhibitor that prevents its self-processing and secretion and so delivers an effect similar to those of PCSK9 loss-of-function mutations. As plasma LDLR binding and receptor dependent endocytosis probably the rate-determining step for PCSK9 function, antibodies or small molecules that bind plasma PCSK9 and disrupt its association to LDLR may also be effective inhibitors of PCSK9 function. Our structure reported here, and ultimately that of the PCSK9-LDLR complex, will be valuable for designing novel therapies.” (C8, p. 418, underline CD)*

8.54 Based on the above, the Central Division comes to the conclusion that at the priority date, the skilled person would have derived from Lagace, that PCSK9 was secreted from the cell and that the secreted form interacted with LDLR and that this extracellular pathway was (if not the physiologically active pathway, at least) physiologically relevant. Against this background, also taking into account the general (commercial) interest in PCSK9 as a target for the treatment of hypercholesterolemia at the relevant date, the skilled person would have been motivated by Lagace to develop antibodies that block the interaction of PCSK9 with the LDLR in order to treat hypercholesterolemia and as a next step would develop such antibodies. Generating and selecting such antibodies was a matter of routine for the skilled person at the relevant date (further discussed below).

8.55 In sum, starting from Lagace, the next obvious step for the skilled person faced having the aim of finding a treatment for hypercholesterolemia and related disorders targeting PCSK9 would be the development of antibodies against PCSK9 that block the LDLR-PCSK9 interaction, thereby ending up with antibodies that fall within the claims of the Patent.

#### **Reasonable expectation of success**

8.56 The Central Division can leave undecided the question of whether or not under the circumstances of the present case, where there is an incentive in the prior art towards the claimed subject matter and the next steps would not amount to more than routine experimentation for the skilled person, a reasonable expectation of success is required to come to the conclusion that the claimed subject matter lacks inventive step. In the present case, the Defendant has not put forward any (technical) problems that the person skilled in the art would not have been able to overcome on the basis of their common general knowledge at the relevant date. The uncertainties raised by the Defendant would not have prevented the skilled person from taking the

obvious next step, i.e. developing PCSK9/LDLR inhibiting antibodies to treat hypercholesterolemia and related disorders, due to insufficient prospects of success (cf. the CoA in NanoString/10x Genomics, p.36 second par.).

8.57 The absence of a reasonable expectation of success (or more in general: nonobviousness) does not follow from the mere fact that other ways of solving the underlying problem are also suggested in the prior art and/or (would) have been pursued by others. The decisive question that has to be answered is whether or not the claimed solution is obvious starting from a realistic prior art disclosure. This means that the fact that Lagace also points in the direction of other “inhibitors” than inhibitory antibodies does not imply that the skilled person would not have pursued the obvious route of antibodies or would have lacked a reasonable expectation to do so. Equally, the fact that Graham (D19) investigated antisense inhibition of PCSK9 and concludes that this is an attractive and novel therapeutic approach for treating hypercholesterolemia in human (Graham, Abstract, last sentence) does not, realistically, mean that the skilled person would not, or with necessarily lower expectations, follow up on the suggestion in Lagace to follow an antibody approach.

8.58 A reasonable expectation of success was also not absent because it was, as argued by the Defendant, not known if extracellular PCSK9 action had any relevance *in vivo*. This argument is rejected on basis of the facts as already established and assessed by the Central Division. Reference is made to the arguments and conclusions reached above, which are not repeated here for conciseness, based on which the Central Division found that the skilled person took from the prior art at the relevant date, in particular from the starting point Lagace, that PCSK9 was secreted from the cell and that the secreted form of PCSK9 interacted with LDLR and that this extracellular pathway was physiologically relevant (*in vivo*).

8.59 Defendant argues that PCSK9 in plasma would have been considered as “*functionally inert*” by the skilled person because of its low binding affinity to LDLR at neutral pH in combination with its plasma concentration (RtCC 9.a). This would amount to a reason why the skilled person would have no reasonable expectation of success to take an antibody approach. However, the existence of such doubts is not supported by the prior art documents relied upon by Defendant. Cunningham (C11), despite the statement referred to by the Defendant in 212 RtCC, concludes that “antibodies ... that bind plasma PCSK9 and disrupt its association to LDLR may also be effective inhibitors” (underline CD). Likewise, Lagace discloses to the skilled person, and Dr. [redacted] as an inventor (see citation above, 8.50) included in a contemporaneous patent application, that extracellular PCSK9 was a promising target indeed whereby Lagace explicitly measured and discussed the plasma levels of PCSK9 in humans. Fischer 2007 (C7) does not say anything that would lead the skilled person to a different conclusion. To the contrary, they conclude: “*Together, the results of our biochemical and cellbased*

*experiments suggest a model in which secreted PCSK9 binds to LDLR and directs the trafficking of LDLR to the lysosomes for degradation.*” (final sentence, Abstract, underline CD).

8.60 It has therefore not been established that the skilled person would see the plasma concentrations of PCSK9 and/or the binding affinity to LDLR at neutral pH as a serious obstacle to developing an antibody treatment for hypercholesterolemia and the related conditions claimed.

8.61 In a similar vein, the Defendant has not made sufficiently plausible that the possible “sequestration” of therapeutic antibodies would have been a real concern for the skilled person who was considering to develop an antibody therapy directed against the PCSK9/LDLR interaction. Sequestration by a “pool of inert PCSK9 in the circulation” (227 DtCC) would according to the Defendant cause the skilled person to doubt that the administration of antibodies would achieve sufficient concentrations at the liver cell surface to have any therapeutic effect. First of all, none of the prior art documents on file mention sequestration of antibodies as a problem, let alone in relation to proposed anti-PCSK9 antibodies. Even if it would be accepted that PCSK9 antibodies would after injection or infusion encounter PCSK9 in the circulation, given the expected relevance of plasma PCSK9 as a therapeutic target (see above), the Defendant has not made clear how such “sequestering” of antibodies by PCSK9 would be anything different from (therapeutically useful) binding to PCSK9 to block its interaction with the LDLR.

8.62 According to the Defendant, the skilled person would furthermore lack a reasonable expectation of success because there would be doubts that antibodies would be able to reach the relevant sites of action at the liver surface due to the architecture of liver cells. The Claimants rebut stating that (to the contrary) the skilled person would have expected a protein expressed in the liver such as PCSK9 to be particularly accessible to antibodies and amenable to antibody therapy. The issue of liver architecture can remain open (whereby the Central Division does note that the claims of the Patent are not limited to a use in the treatment of atherosclerotic vascular disease as the Defendant and Dr. [redacted] seem to wrongfully presume in their rejoinder to Claimants’ reply on this point, see 170 R, with reference to par. 7.1-7.2 E11) as the skilled person would have expected PCSK9 in plasma to be a relevant therapeutic target (as argued by the Claimants, also see above). Accessing the surface of liver cells would therefore not have been considered as a necessity for the skilled person whose aim was to find a treatment of the conditions as defined in the claims.

8.63 There were according to Defendant further doubts because of PCSK9’s presumed high turnover rate *in vivo* (232 DtCC). The existence of such doubts, let alone that these doubts would have affected the skilled person’s reasonable expectation of success at the relevant date has not been adequately substantiated by the Defendant, especially given Claimants’ responses. Document D23 (“Grefhorst”) which is relied upon in this context does

not form part of the prior art and therefore cannot – without further explanation which is lacking – contribute to the skilled person's expectations on the relevant date. It has furthermore not been disputed by the Defendant that antibodies against protein targets having a high turnover rate in vivo, such as TNF- $\alpha$ , were commonly known and had been successful in the clinic before the relevant date. Even if it would be accepted that the skilled person would realise that antibodies were not a "panacea for neutralizing proteins with high turnover rates" (181 DtCC) and even if the knowledge about antiTNF- $\alpha$  antibodies would have been regarded as irrelevant as argued by the Defendant, this in any event does not support the conclusion, that at the relevant date there would be no reasonable expectation of success for the skilled person absent any concrete information about the turnover rate of PCSK9 and the conclusions the skilled person would draw therefrom in the prior art.

8.64 Finally, the Defendant argued that there were doubts that antibodies binding to the catalytic domain could disrupt PCSK9/LDLR interaction. In this respect, the Central Division does not attach weight to the statement in a Schering patent application (C38, filed on 27 October 2008 with a priority date of 26 October 2007, published 30 April 2009) that finding a blocking antibody would be unlikely given the large sizes of the proteins PCSK9 and LDLR. In any event, C38 was published on 30 April 2009 and is not part of the prior art and therefore cannot "teach away" as argued by the Defendant (236 DtCC). The Central Division also does not see how Zhang (C4) would teach away from the claimed subject matter. First of all, Zhang (from the same research group as Lagace and Horton) confirms to the skilled person that recombinant human PCSK9 binds the LDLR on the surface of cultured hepatocytes and promotes degradation of the receptor after internalization (see Abstract), in other words: the extracellular pathway. The research of Zhang adds to previous publications that the binding site of PCSK9 on LDLR was localised to the EGFa domain of LDLR (Abstract). If anything, the teaching of Zhang would confirm to the skilled person that blocking the LDLR-PCSK9 interaction, as suggested by Lagace, (with the additional knowledge that PCSK9 interacts with the EGFa domain within the extracellular domain of the LDLR) was indeed a promising avenue to pursue. The fact that Zhang used a non-blocking polyclonal antibody as a research tool (for immunoprecipitation) has no bearing on the reasonable expectation of success of the skilled person to generate (therapeutically useful) blocking monoclonal antibodies. The Central Division also fails to see why Cunningham (C8) and Piper (C12) would teach away by suggesting that other domains from PCSK9 may be important for the PCSK9/LDLR interaction, already for the reason that the claimed antibodies are not limited to antibodies that bind solely to the catalytic domain and cover antibodies that (in addition to binding to the catalytic domain) bind to the pro and V-domain of PCSK9 as well.

8.65 In conclusion, the arguments by the Defendant as to why the skilled person would have no reasonable

expectation of success to find antibodies against PCSK9 that inhibit the interaction between PCSK9 and LDLR and thereby find a treatment for hypercholesterolemia must fail.

*The skilled person would arrive at antibodies falling under the claim*

8.66 Defendant argued (in an auxiliary way) that even if the skilled person would have started a research program to develop antibodies against PCSK9, the result would not inevitably have led to one that is within the scope of claim 1 (par. 301 et seq. DtCC, par. 2 reply in the CC dated 21 March 2024).

8.67 As a preliminary point, the Central Division is of the opinion that for assessing inventive step it is not the question whether the skilled person would inevitably, i.e. invariably each and every time they are set out on a particular course of action based on the prior art, arrive at the same result (falling within the scope of the claim or not). Rather, it is sufficient (but also necessary) for denying inventive step that the skilled person would without inventive contribution arrive at a result which is covered by the claim. In the present case, ending up with antibodies that fall under the scope of the claims of the Patent, including antibodies that bind to the catalytic domain of PCSK9, was obvious.

8.68 It is not in dispute that at the priority date, the skilled person generally knew how to generate (monoclonal) antibodies to a given protein target and that such antibodies could be screened functionally for their ability to inhibit the interaction between the target and another protein such as a receptor in an appropriate assay. The skilled person would have realised that making antibodies and setting up the screening methods may require considerable time and resources, but to do so does not constitute an "undue burden" in patent law terms. Accordingly, the Patent mentions in par. [0201]-[0210] several methods to generate (monoclonal) antibodies. These methods include phage display technology, hybridoma technology and the use of transgenic mice. It is also not in dispute between the parties that these methods were known and routine at the priority date (cf. the technical background section above and E6, par. 39-41).

8.69 It is furthermore not in dispute that the catalytic domain of PCSK9 could not be expressed and purified in isolation. According to the Defendant, the entire PCSK9 protein can be used as an antigen to immunize the transgenic mice as demonstrated in the Patent (292 et seq. R, also see 64 Case summary). Accordingly, the skilled person would have used the whole PCSK9 protein as an antigen to obtain anti-PCSK9 antibodies in following Lagace's suggestion to develop antibodies against PCSK9 that block the interaction between LDLR and PCSK9.

8.70 After generating antibodies against PCSK9 using any of the above methods (whereby the Central Division reiterates that the claims are not limited to any particular method of generating antibodies), the next step will be to screen antibodies to confirm binding to PCSK9 and for their activity to block the interaction of PCSK9 and the LDLR. As mentioned above, it is not in dispute that



these steps of finding selecting antibodies that bind to a particular target and are functionally active were, as such, routine steps and that the skilled person at the priority date (and long before) was in a position to carry out these without undue burden. See e.g. the Defendant in par. 350 DtCC (in the context of sufficiency of disclosure) comparing EPO Technical Board of Appeal case T431/96 to the present case:

*“6. The written description of how hybridomas secreting a monoclonal antibody with the desired features have been produced consists basically of the sequence of the widely known routine technical steps where all that is normally called for is perseverance. As the said monoclonal antibody is characterised by its reactivity/non-reactivity with given products (cf. claim 1), this being readily testable in an assay, the skilled person seeking to reproduce the invention will have to produce monoclonal antibodies by routine methods and test them singly in an assay. This may possibly involve some tedious and time-consuming work, but nothing out of the ordinary since the techniques for the production and selection of hybridomas were common routine techniques at the priority date of the patent in suit (i.e. 17 March 1983).”*

#### **The methods used by the Defendant**

8.71 In the DtCC and R, Defendant argued that despite the level of skill in the antibody arts and the ‘routine’ assays available, the specific steps and experimental design used by the Defendant’s inventors were anything but routine and were apparently crucially important in identifying the class of PCSK9 antibodies disclosed in the Patent (e.g. 304 DtCC). Defendant refers to the antibody generation and screening protocols which are disclosed in the Patent and were “critical for success” (with reference to D93, the declaration of Mr. Pan, an employee of the Defendant, who was involved in the PCSK9 project as of July 2006). The steps referred to by the Defendant mainly relate to the immunisation protocol and the immobilisation method for PCSK9 used for screening. At the oral hearing, the Defendant for the first time took the position that the skilled person would not have found antibodies falling under the claim using routine methods.

8.72 Leaving aside the late point in time that the Defendant adopted this position and the objections raised to this by the Claimants, the Central Division is not convinced that the immobilisation techniques employed by Defendant go beyond techniques that the skilled person would have routinely employed at the relevant date. Claimants have convincingly argued that biotinylation was a standard, if not the most commonly used, method for immobilising antigens in antibody screening at the relevant date (1.2 RtD CC). The fact that the Defendant first tried two other (common) ways of immobilising PCSK9, which apparently did not work, does not change the fact that biotinylation was a standard method. Therefore, even if immobilisation of PCSK9 by biotinylation were necessary to be able to successfully screen for the desired anti-PCSK9 antibodies, which is

disputed by the Claimants, this step (which the Central Division notes is not part of the claims of the Patent) cannot amount to an inventive step.

8.73 In relation to the immunisation protocol that was used rendering the claim non-obvious, this argument fails already for the reason that it was routinely known for the skilled person how to obtain antibodies against PCSK9 without immunisation using the phage display method. The phage display method belonged to the common general knowledge and is also mentioned in the Patent as a technique that can be used to generate monoclonal antibodies in accordance with the invention (see par. [0201], [0205] and [0211] of the Patent). The pharmaceutical company Merck in fact successfully produced antibody 1D05 using phage display which antibody according to the Claimants— and not (specifically) contested by the Defendant – meets the requirements of the Patent claim which is not limited to antibodies raised using any particular kind of immunisation method.

8.74 Furthermore, even if it were accepted in favour of the Defendant that the inventors of the Patent took a non-routine approach and obtained the results (functional antibodies) included in the Patent, this does not mean that the skilled person would not arrive at an antibody falling under the scope of the Patent claims using routine methods of antibody generation and selection as the Claimants have credibly argued supported by references to the common general knowledge (see e.g. 3.2.8 CC, 2.11 Case Summary) and as also follows from the above discussion.

8.75 Defendant argued that other pharmaceutical companies used other methods and ended up with antibodies against PCSK9 that do not or less effectively block PCSK9/LDLR interaction (e.g. 43 R). Defendant also pointed out that antibody 31A4 binds to the V-domain of PCSK9 and, according to the Patent, does not inhibit LDLR binding to PCSK9 but does display significant PCSK9 neutralizing ability (see par [0500]-[0501] of the Patent description, Comparative Example 41). This, however, does not imply that the skilled person, in view of the teaching of Lagace, would not have arrived at the PCSK9/LDLR blocking antibodies as claimed using routine techniques. As set out above in the discussion of the legal framework for inventive step (8.4), an objective approach to inventive step must be taken. It is only relevant what the claimed invention actually contributes to the prior art.

#### **“Binds to the catalytic domain”**

8.76 Specifically in relation to the feature “binds to the catalytic domain of a PCSK9 protein” (F.3), Claimants have argued that this feature is arbitrary and does not give rise to any particular advantages or useful technical effects (CC 202, 2.18 Case Summary). Defendants have argued that binding to the catalytic domain was not obvious.

8.77 The skilled person, starting from the teaching of Lagace, who would take the step to develop antibodies against PCSK9 that inhibit LDLR interaction, would generate and screen antibodies using the full PCSK9 protein, so including the pro-, catalytic and V-domains,

as also done in the Patent (see above 8.69). Especially in view of the interpretation of the term “catalytic domain”, which requires the antibody to bind to at least one amino acid residue that lies within the catalytic domain (being one of three domains, spanning amino acids 123-419 out of a total of 662 amino acids) and which term is not limited to antibodies that bind exclusively (or even predominantly) to amino acid residues that lie within the catalytic domain, the so generated antibodies would in all likelihood encompass antibodies that “bind to the catalytic domain”. In addition, the claimed antibodies are not limited to a particular way of blocking the PCSK9/LDLR interaction. As long as the anti-PCSK9 antibodies block the interaction between the LDLR and PCSK9, as suggested by Lagace, they would “pass the screen” and would meet the functional requirements of the claim. There would have been no technical reason for the skilled person to (include or) exclude any (functional, inhibiting) antibodies based on their binding location. This is already evidenced by “reference antibody” 31H4 which binds to the catalytic domain and to the pro-domain. Conversely, as acknowledged by the Defendant, not all antibodies that bind to the catalytic domain will block PCSK9/LDLR binding and/or will have a therapeutic effect (R, 51). There is furthermore no teaching in the prior art that leads the skilled person away from antibodies binding to the catalytic domain (see above par. 8.64).

8.78 As also discussed under claim interpretation (see par. 6.20 above), there is no apparent causal technical connection between the feature “binds to the catalytic domain” and the reduction of the binding of PCSK9/LDLR and, ultimately, the therapeutic effect claimed. The Central Division is therefore of the opinion that the feature of binding to the catalytic domain cannot contribute to inventive step. The skilled person knew at the relevant date that PCSK9 consisted of three domains. Specifying that the antibodies bind to the catalytic domain as interpreted by the skilled person, is an arbitrary choice out of several possibilities that cannot render the claimed subject matter inventive.

8.79 Finally, none of the parties have argued that there would be any inventive skill required to test the obtained antibodies in a mouse model to confirm that the antibody can be used to treat the conditions that were commonly known to be associated with elevated cholesterol levels, thereby arriving at the claimed use.

#### **Conclusion on inventive step**

8.80 Based on the above, the Central Division concludes, after weighing all relevant aspects, that the skilled person at the relevant date would have followed-up on the explicit suggestion in Lagace and would have developed anti-PCSK9 antibodies as a treatment for hypercholesterolemia and – doing so – would have arrived at the (uses of) antibodies as claimed.

8.81 The unknowns and uncertainties that were brought forward by the Defendant, none of which are clearly voiced in the many prior art documents relied upon in this case, in any event do not outweigh the clear incentive provided by Lagace to develop anti-PCSK9 antibodies that block the interaction between PCSK9

and LDLR for treatment of hypercholesterolemia and cardiovascular atherosclerotic disease, especially against the background that PCSK9 was seen as a very promising target for the treatment of these diseases at the relevant date. The skilled person would have developed such antibodies using routine techniques.

8.82 In summary, the skilled person would, starting from Lagace as a realistic starting point in the prior art, arrive at the claimed subject matter without inventive skill. This means that claim 1 of the Patent as granted (Main Request) is invalid due to a lack of inventive step.

#### **9 Main request invalid: subclaims and application to amend**

9.1 Claimants have argued that and have substantiated why the dependent claims 2-11 do not contain any features that contribute to inventive step. As the Defendant has not replied to this, and it is not apparent to Central Division why it should find otherwise, claims 2-11 of the Main Request lack inventive step for the same reasons as claim 1 of the Patent. Accordingly, the Main Request must be held invalid in its entirety for lack of inventive step.

#### **Application to amend (auxiliary requests)**

9.2 The Defence to Revocation in the Revocation action and the Defence to the Counterclaim for Revocation in the Infringement action both include the same conditional application to amend the Patent (**Rule 30 RoP** which applies mutatis mutandis in a revocation action based on **Rule 50 RoP**). Various amendments were proposed by way of multiple alternative sets of claims (auxiliary requests 1-17 divided in five different “sets” of auxiliary requests).

9.3 The Claimants have not argued that the Defendant’s application to amend does not meet the requirements of **Rule 30.1 RoP**. The Central Division sees no reason to find otherwise. The application to amend is therefore admissible.

9.4 The Claimants have raised several objections in relation to the requirements of Articles 84 and 123(2) EPC. It is not necessary for the Central Division to decide on these objections since the proposed claim amendments cannot in any event remedy the lack of inventive step found for the Main Request.

9.5 The proposed amendments were summarised by the Defendant as follows (Table 1, DtR, same Table 3 DtCC):

Table 1: Summary of Auxiliary Requests

	Set 1	Set 2 deletion of the third therapeutic use in claim 1 (and corresponding deletion of dependent claim 5)	Set 3 deletion of the second and third therapeutic uses in claim 1 (and corresponding deletion of dependent claims 2 to 5)	Set 4 deletion of the second and third therapeutic uses as in Set 3, and binding to the catalytic domain defined by amino acids 153-449	Set 5 deletion of the second and third therapeutic uses as in Set 3, and binding at a location within amino acids 153-447
-	MR			AR10	AR14
deletion of dependent claims 6 and 7	AR1	AR4	AR7	AR11	AR15
deletion of dependent claim 8 and further deletion of "fragment"	AR2	AR5	AR8	AR12	AR16
deletion of dependent claims 6 to 8 and further deletion of "fragment"	AR3	AR6	AR9	AR13	AR17

9.6 As follows from the submissions of the Defendant, auxiliary requests AR1- AR9 (sets 1, 2 and 3) were filed to address various added matter objections raised by the Claimants (478 DtR). Auxiliary requests AR10-AR13 (set 4) were filed to address the priority attack (481 DtR). Auxiliary requests AR14-AR17 were also filed to address the priority attack (484 DtR).

9.7 The Central Division found that the claims of the Patent as granted (Main Request) lack inventive step. However, as can be seen from the Defendant's submissions, none of the Auxiliary Requests has been submitted to address a lack of inventive step. As regards inventive step, the Defendant has merely stated that the claims of the auxiliary requests are inventive for the same reasons as the Main Request without providing any further explanation. Despite the extensive debate between the parties on (claim interpretation and) inventive step, at no point did the Defendant submit – and it is not apparent to the Central Division – that and how any of the auxiliary requests could serve as a basis for revocation of the Patent in part considering a lack of inventive step of the Main Request. Therefore, also taking into account [Article 76 UPCA](#), according to which a decision on the merits may only be based on grounds, facts and evidence, which were submitted by the parties, the Central Division concludes that Auxiliary Requests 1-17 lack inventive step for the same reasons as the Main Request.

9.8 As a consequence, the Patent is invalid in its entirety and is revoked accordingly. Given that the Patent is revoked on the ground of (lack of) inventive step, there is no need for the Central Division to reach a decision on the other grounds for invalidity raised by the Claimants.

## 10 Conclusion

10.1 In conclusion, as the Main Request nor any of the Auxiliary Requests brought forward by the Defendant is valid, the Patent is revoked entirely, on the ground of Article 138 (1) sub a in connection with Article 56 EPC (Article 65(2) UPCA), for all of the Contracting Member States in which the Claimants have requested revocation.

## 11 Costs

11.1 In accordance with [Article 69 UPCA](#) and [Rule 118.5 RoP](#) the Defendant, as the unsuccessful party, the

Patent being revoked entirely, has to bear the legal costs of the Claimants. The parties have agreed prior to the oral hearing as clarified at the oral hearing that they deem an amount of 1.375 million euro to be reasonable and proportionate (per action for the Revocation Action and the Counterclaim, respectively). The Court understands that the Parties request a (final) decision on the costs to be awarded.

11.2 Given the value of this case (set at 100 million euro, see Order to combine cases dated 27 February 2024, reference in footnote 2) and the corresponding ceiling for recoverable representation costs (up to 2 million euro, see AC Decision on the Scale of Ceilings for Recoverable Costs dated 23 April 2023, D - AC/10/24042023\_E) and the explanations of the parties during the oral hearing, the Central Division has no reason to doubt that the number agreed between the parties is indeed reasonable and proportionate. Accordingly, the Court decides on costs as per the below.

## DECISION

Having heard the parties on all relevant aspects of the case, the Central Division:

1. Revokes European Patent 3 666 797 B1 entirely with effect to the territory of Austria (AT), Belgium (BE), Bulgaria (BG), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Germany (DE), Italy (IT), Latvia (LV), Lithuania (LT), Luxembourg (LU), Malta (MT), The Netherlands (NL), Portugal (PT), Slovenia (SI) and Sweden (SE).
2. The Defendant as the unsuccessful party shall bear the legal costs incurred by the Claimants to an amount of 1.375 million euro.
3. Dismisses any further request made.

## NAMES AND SIGNATURES

### Judges

Presiding judge: Ulrike Voß

Legally qualified judge and judge-rapporteur: Andrés Kupecz

Technically qualified judge: Casper Struve

For the Deputy-Registrar Natalie Gnaß

[...]

### Information about appeal

An appeal against the present Decision may be lodged at the Court of Appeal, by any party which has been unsuccessful, in whole or in part, in its submissions, within two months of the date of its notification (Art. 73(1) UPCA, R. 220.1(a), 224.1(a) RoP).

### Information about enforcement

Art. 82 UPCA, Art. Art. 37(2) UPCS, R. 118.8, 158.2, 354, 355.4 RoP. An authentic copy of the enforceable decision will be issued by the Deputy-Registrar upon request of the enforcing party, R. 69 RegR.

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