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**Datasheet for the decision
of 28 March 2023**

Case Number: T 0835/21 - 3.3.08

Application Number: 12188230.2

Publication Number: 2567709

IPC: A61K39/395, A61P35/00,
C07K16/28

Language of the proceedings: EN

Title of invention:

Molecules and methods for modulating low-density-lipoprotein
receptor-related protein 6 (LRP6)

Patent Proprietor:

Novartis AG

Opponents:

Boehringer Ingelheim RCV GmbH & Co KG /
Boehringer Ingelheim International GmbH (opposition withdrawn)
Merck Patent GmbH

Headword:

LRP6 antibodies/BOEHRINGER INGELHEIM

Relevant legal provisions:

EPC Art. 54, 56, 76(1), 83, 123(2)

Keyword:

Novelty - (yes)

Inventive step - could-would approach

Sufficiency of disclosure - reproducibility (yes)

Divisional application - added subject-matter (no)

Amendments - allowable (yes)

Decisions cited:

T 0601/05, T 0544/12



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Case Number: T 0835/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 28 March 2023

Appellants: - opposition withdrawn -
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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 12 April 2021
rejecting the opposition filed against European
patent No. 2567709 pursuant to
Article 101(2) EPC**

Composition of the Board:

Chair T. Sommerfeld
Members: A. Schmitt
 L. Bühler

Summary of Facts and Submissions

- I. The appeals lodged by opponents 1 and 2 lie from the decision of the opposition division to reject the oppositions to European patent No. 2 567 709 (hereinafter "the patent").
- II. The patent was granted on European patent application No. 12 188 230.2 (hereinafter "the application"), which was a divisional application from European patent application No. 08 844 924.4, filed on 31 October 2008 as an international patent application published as WO 2009/056634 (hereinafter "the earlier application").
- III. The opposition proceedings were based on the grounds for opposition in Article 100(a) EPC in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and on those in Article 100(b) and (c) EPC.
- IV. On 16 December 2021, opponents 1 withdrew their opposition and ceased to be a party to the proceedings.
- V. In reply to the appeals, the patent proprietor (respondent) filed sets of claims of auxiliary requests 1 to 3 which were identical to the sets of claims of auxiliary requests 1 to 3 that had been filed on 22 February 2019 during opposition proceedings.
- VI. The board summoned the parties to oral proceedings, as they had requested, and issued a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion.

VII. As previously announced in writing, the appellant did not attend the oral proceedings. During the oral proceedings, the respondent withdrew the main request and renumbered the auxiliary requests 1, 2 and 3 that had been submitted with the reply to the appeal as main request, auxiliary request 1 and auxiliary request 2 respectively. At the end of the oral proceedings, the chair announced the board's decision.

Claims 1, 8 and 9 of the main request read as follows.

"1. A monoclonal antibody or an antigen-binding fragment thereof that specifically binds to human low-density-lipoprotein receptor-related protein 6 polypeptide (LRP6) having the amino acid sequence of SEQ ID NO:1, is capable of antagonizing the Wnt signaling pathway, and inhibits Wnt3- and Wnt3a-specific signaling activity, wherein the antigen binding portion binds to an epitope of human LRP6 within amino acids 631-932 of SEQ ID NO:1 as shown in Table 1.

8. A pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment of any of the preceding claims.

9. The monoclonal antibody or antigen-binding fragment of any one of claims 1 to 7 or the pharmaceutical composition according to claim 8 for use in treating cancer, wherein the use comprises administering the antibody, the antigen-binding fragment, or the pharmaceutical composition to a subject suffering from or afflicted with cancer."

VIII. The following documents are referred to in this decision.

- D2 S. A. Ettenberg et al., PNAS 107(35), 2010, 15473-15478
- D5 Y. Gong et al., PLoS One 5(9), 2010, e12682
- D6 US 2005/070699 A1
- D7 US 2004/244069 A1
- D8 L. Li et al., J Biol Chem 277(8), 2002, 5977-5981
- D9 Y. Li and G. Bu, Future Oncol. 1(5), 2005, 673-681
- D10 WO 2006/055635
- D11 B. Mao et al., Nature 411, 2001, 321-325
- D14 Y. Zhang et al., Mol Cell Biol 24, 2004, 4677-4684
- D15 US 2005/0196349 A1
- D17 Z. Khan et al., Mol Cell Biol 27, 2007, 7291-7301
- D31 Declaration by Feng Cong, Ph.D., 22 April 2020
- D40 M. Katoh, International Journal of Molecular Medicine 9, 2002, 579-584
- D41 M. Katoh, International Journal of Oncology 19, 2001, 977-982

IX. The appellant's arguments, where relevant to the decision, are summarised as follows.

Main request - claim 1

Amendments (Article 76(1) EPC and Article 123(2) EPC)

Claim 1 of the application (claim 4 of the earlier application) contained two alternatives for the LRP6 amino acid region to which the antibody bound, and stated that the binding was "within or overlapping" this region. From this disclosure, the features "within" and "amino acids 631-932 of SEQ ID NO:1" were

separately selected from two different lists of equivalent alternatives, which, in the absence of a pointer, was not allowable. Paragraphs [0013], [0215], [0232] and [0235] of the application disclosed these features only in combination with further limitations or in a more specific context and so could not serve as a basis for the claimed subject-matter either. An intermediate generalisation from these passages was not allowable.

The application did not disclose that the LRP6 binding molecule was a "monoclonal antibody or an antigen-binding fragment thereof" as recited in claim 1 of the main request. Claim 1 of the application (claim 4 of the earlier application) only disclosed that the LRP6-binding molecule comprised "an antigen binding portion of an antibody". Claim 17 of the application (claim 20 of the earlier application) only disclosed that the antigen-binding portion was that of a monoclonal antibody. These claims thus only defined the antigen-binding portion. Paragraph [0010] of the application did not mention antigen-binding fragments of a monoclonal antibody that specifically bound to human LRP6.

Claim construction - claim 1

The expression "inhibits Wnt3- and Wnt3a-specific signaling activity" meant that the claimed antibody inhibited the signalling by Wnt3 and Wnt3a over any other Wnt ligands, i.e. the claimed antibody itself had to be Wnt3- and Wnt3a-specific. This claim construction corresponded to the meaning and scope of the term "specific" in its ordinary meaning and was in line with the general teaching in the application with respect to the claimed binding molecules, as evident from

paragraphs [0015], [0038] and [0231] to [0237] of the application.

The expression "capable of antagonizing the Wnt signaling pathway" required the claimed antibody to have a net antagonistic effect on the Wnt signalling pathway, irrespective of any other Wnt ligand that might be present in a cell. This feature hence defined an additional property of the claimed antibody to the inhibition of Wnt3- and Wnt3a-specific signalling activity. This condition was not already fulfilled by the antibody's inhibiting of Wnt3- and Wnt3a-specific signalling activity, as other Wnt ligands present in the cell might still activate this pathway, leading to net activation of the pathway.

Sufficiency of disclosure (Article 83 EPC)

Claim 1

The feature that the claimed antibody or antigen-binding fragment inhibited "Wnt3- and Wnt3a-specific signaling activity" was so unclear that a skilled person would not know how to reproduce it without undue burden. The application did not specify any threshold or cut-off level for Wnt3- and Wnt3a-inhibition, or what levels of inhibition were Wnt3- and Wnt3a-subtype-specific by comparison with the inhibition of other Wnt subtypes. Even if only a preferential inhibition of the Wnt3- and Wnt3a-specific signalling activity over the signalling activity by other Wnt ligands was required by the claim, the skilled person could not know where the boundaries of the claimed subject-matter were and hence whether or not they had obtained an antibody that fulfilled this requirement.

The functional definition of the claimed antibody or antigen-binding fragment resulted in a reach-through claim, in which the disclosure in the application merely amounted to instructions for a new research project. The application did not contain a single reproducible example, or any verifiable data. The identity of none of the "Fabs", including the control Fab, was disclosed, nor how the alleged percentage of Wnt inhibition in Table II or the binding events in Table III had been calculated. No link was disclosed between the compounds tested in Tables II and III; there were no figures in the application.

The only compounds of the application which allegedly bound to the propeller 3 domain and provided Wnt3- and Wnt3a-specific inhibition were the antibody fragments designated "Fab002" and "Fab004". The application did not disclose any structural information or information on the epitope of these antibody fragments. It was not even clear that they bound to the propeller 3 domain of LRP6, since there were alternative explanations for the loss of binding of these antibody fragments to LRP6 upon deletion of the propeller 3 domain, such as incorrect folding of the remaining propeller domains.

Even if Fab002 and Fab004 were considered to bind within amino acids 631 to 932 of LRP6, a preferential Wnt3 and Wnt3a inhibition was only disclosed for Fab004 (Table II of the application). A broadly generalised concept could not be derived from a single unreproducible example.

It was not true that all Wnt3- and Wnt3a-specific LRP6-inhibitory antibodies bound to the propeller 3 domain of LRP6, as was evident from document D8; nor was it true that all antibodies that bound to LRP6's

propeller 3 domain provided Wnt3- and Wnt3a-specific inhibition, as was evident from the LRP6 agonist antibody fragments designated "Fab025" and "Fab026", disclosed in paragraphs [0235] and [0236] of the application. Hence, no link existed between the two functional characteristics of the claimed antibody or antigen-binding fragment thereof.

Since there was no direct relationship between binding to the propeller 3 domain and Wnt3- and Wnt3a-specific inhibition, the skilled person would have to screen a starting antibody mixture for both binding to an epitope within amino acids 631 to 932 of SEQ ID NO:1 and inhibition of Wnt3- and Wnt3a-specific signalling activity. The number of starting compounds to be tested was too large to be tested systematically, and the skilled person was not in possession of any reproducible example as a positive control. The skilled person was thus faced with an unreasonable amount of trial-and-error testing, and therefore could not provide the claimed antibodies without undue burden (T 544/12, points 4.3 and 4.8 of the Reasons).

Claim 9

It was not denied that an antibody which antagonised the Wnt signalling pathway could be used in the treatment of cancer. However, the claimed antibodies were not capable of antagonising the Wnt signalling pathway in general, since they did not have a net effect on Wnt signalling and even potentiated Wnt1-induced signalling activity when they were in a bivalent IgG format (Example 4 of the patent). Post-published document D2 could not be relied on for sufficiency of disclosure, since such disclosure was assessed as at the priority date. In any case,

document D2 only disclosed results on specific Wnt3-dependent xenograft mouse models and therefore did not support the assertion that the Wnt signalling pathway in general, in any cell, could be antagonised by the claimed antibody.

Novelty (Article 54 EPC) - claim 1

Document D6 disclosed the preparation of single-chain variant fragments (scFvs) against LRP5 and LRP6 using synthetic LRP5- and LRP6-derived peptides in a phage display screen (paragraph [0439] ff.). The synthetic peptides included two which were within the propeller 3 domain of LRP6 as recited in the claim (Table 12 of document D6) and hence bound to an epitope of human LRP6 as defined in the claim. Document D6 also disclosed the use of a peptide from the propeller 3 domain of LRP6 for the generation of a polyclonal antibody (paragraph [0433] and Table 11 of document D6). Since a polyclonal antibody was a collection of monoclonal antibodies, Table 11 implicitly disclosed a monoclonal antibody that bound to the propeller 3 domain of LRP6.

According to the teaching of the application, an antibody or antigen-binding fragment thereof that bound to an epitope within or overlapping with amino acids 889 to 929 and 767 to 805 of LRP6 was particularly likely to inhibit Wnt3- and Wnt3a-specific signalling (paragraph [0013], item (a) and paragraph [0014], item (d) of the application). Since the scFvs of document D6 bound within amino acids 908 to 828 or 768 to 788 of LRP6, it was highly likely that they also inhibited Wnt3- and Wnt3a-specific signalling activity.

It was not relevant that document D6 did not explicitly disclose that the disclosed LRP6-specific scFvs and antibodies inhibited Wnt3- and Wnt3a-specific signalling activity, because the burden of proof to demonstrate that this was not inherently the case lay with the respondent. In fact, if an antibody was exclusively defined by functional features and the prior art disclosed an antibody directed to the same antigen, it had to be assumed that the prior-art antibody had the same functional properties as the claimed antibody (EPO Guidelines G-II 5.6.1.3, second paragraph).

Moreover, the Wnt3- and Wnt3a-specific inhibition was such an unusual functional parameter that it could not be expected that prior-art documents had tested for its presence or absence (EPO Guidelines G-II 5.6.1.3). Since the respondent had not provided any evidence that the LRP6-specific scFvs and antibodies of document D6 did not inhibit Wnt3- and Wnt3a-specific signalling activity, the claimed antibody or antigen-binding fragment thereof lacked novelty over those disclosed in document D6.

Document D7 also disclosed scFvs against LRP5 and LRP6 (paragraph [0404] ff.) which bound to an epitope within propeller 3 as defined in the claim (the table in paragraph [0406] of document D7). The subject-matter of claim 1 was not novel over these scFvs for the same reasons that it was not novel over the scFvs disclosed in document D6.

Document D8 disclosed a monoclonal LRP6 antibody that inhibited Wnt3a-induced signalling activity (last paragraph of left-hand column and first paragraph of right-hand column of page 5979 and Figures 4A and 4B of

document D8). This antibody had been raised against a peptide from the propeller 2 domain of LRP6 that only differed from a peptide within the propeller 3 domain of LRP6 in three conservative substitutions. It was therefore highly likely that this antibody also bound to the propeller 3 domain of LRP6. Since the claimed antibody was only defined by functional features, the burden of proof that this antibody did not bind to the propeller 3 domain lay with the respondent. In the absence of such proof, the claimed subject-matter was not novel over the antibody of document D8.

Inventive step (Article 56 EPC)

Document D8 and documents D6 or D7 were equally suitable as starting points for the assessment of inventive step.

Document D8 as closest prior art

The claimed antibody differed from the antibody disclosed in document D8 only in that it bound to an epitope in the propeller 3 domain of LRP6. In the absence of comparative data, no technical effect could be attributed to this difference. The objective technical problem was the provision of an alternative Wnt3- and Wnt3a-specific inhibitory LRP6 antibody.

A skilled person faced with this problem would screen for other Wnt3- and Wnt3a-inhibiting LRP6 antibodies by routine methods. It was routine to obtain an antibody against any domain of LRP6, including the propeller 3 domain. In the absence of a technical effect, targeting a specific propeller domain was an arbitrary choice. The skilled person was not limited to antibodies binding to the propeller 2 domain, as disclosed in

document D8, but would probably rely on an unbiased screening. The Wnt antagonist Dkk1 was for example known to bind to propeller 3 of LRP6. Blocking the Wnt binding site on LRP6 was not the only way an LRP6 antibody could affect Wnt signalling. Structural changes to LRP6 upon antibody binding, or indirect mechanisms, were also a possibility.

The screening would probably result in LRP6 antibodies binding within and outside of the propeller 3 domain of LRP6, but this was irrelevant to the fact that such screening was not inventive. No motivation to select a specific alternative was required in order to fulfil the provisions of the claim; rather, it was sufficient that antibodies having the features recited in the claim would be among the available alternatives, because a feature that had no technical effect was arbitrary.

Documents D6 or D7 as closest prior art

Document D6 disclosed antibodies targeting various epitopes in the LRP6 propeller 3 domain. The only difference that could be seen from the claimed antibody was that these documents did not explicitly recite that the disclosed antibodies inhibited Wnt3- and Wnt3a-specific signalling activity. The objective technical problem was the provision of an antibody that inhibited Wnt3- and Wnt3a-specific signalling activity. No motivation to provide antibodies that inhibited Wnt3- and Wnt3a-specific signalling activity was required; however, such motivation was present in any case because of the general motivation in the art to find LRP6-antagonising antibodies, in view of the common general knowledge on the Wnt ligand's role in human cancers. To solve the technical problem, the skilled

person would test the antibody fragments of document D6 and, if they did not have this property, would screen for other LRP6-binding antibodies that did. The screening procedure was mere routine; thus, it was straightforward to obtain such antibodies.

The skilled person reasonably expected to succeed in providing such antibodies, since they knew from paragraphs [0176], [0177] and Figure 45 of document D6 that there were positions in propeller 3 and 4 of LRP6 that, when bound, could cause inhibition of Wnt signalling and in particular Wnt3a signalling, since Dkk1 bound at these positions and specifically inhibited Wnt3a-mediated Wnt signalling. The binding of these antibodies within amino acids 631 to 932 of LRP6 was an arbitrary choice devoid of any specific technical effect.

Since the disclosure in document D7 was similar to that in document D6, the same considerations applied. The claimed subject-matter was therefore not inventive in view of the disclosure in document D6 or document D7.

- X. The respondent's arguments, where relevant to the decision, are summarised as follows.

Main request - claim 1

Amendments (Article 76(1) EPC and Article 123(2) EPC)

The claimed monoclonal antibody or antigen-binding fragment thereof had a basis in claims 4, 7 and 20 of the earlier application and corresponding claims 1, 4 and 17 of the application. The subparts (a) and (b) of claim 4 were not mutually exclusive equivalent alternatives within a list of possibilities. Although these claims only referred to an antigen-binding

portion of an antibody, complete antibodies had a basis in paragraphs [0010], [0026], [0027], [0083] and [0193] of the application and the earlier application. The link between binding to propeller 3 of LRP6 and inhibition of Wnt3- and Wnt3a-specific signalling activity was present in the last sentence of paragraph [0034] and in paragraphs [0235] and [0236] of the application and the earlier application.

Claim construction

The wording "inhibits Wnt3- and Wnt3a-specific signaling activity" recited in the claim did not require that the antibody was an exclusive inhibitor of Wnt3 and Wnt3a signalling activity. The claimed binding molecules were allowed to demonstrate some inhibition of the signalling activity induced by other Wnt ligands, such as Wnt1.

This interpretation was consistent with the synonymous use of the terms "specific" and "preferential" in the patent (paragraphs [0009], [0020], [0176], [0177], [0180], [0181]) and the data in Table II, which showed that Wnt3a-specific binding molecules (Fab003, Fab004, Fab023) preferentially, but not exclusively, inhibited the signalling activity induced by Wnt3 and Wnt3a compared to the Wnt1 class of ligands. To construe the claim such that an exclusive inhibition of Wnt3 and Wnt3a signalling was required would go against scientific knowledge and the teaching in the patent, and therefore against the requirement that the claimed subject-matter should be interpreted in a technically sensible manner, taking into account the entire disclosure of the patent.

The overall disclosure of the patent did not suggest that the claimed antibodies were required to have a net antagonistic effect across all types of Wnt ligands. This was evident from paragraph [0009] of the patent. The feature of inhibiting Wnt3- and Wnt3a-specific signalling activity was sufficient to fulfil the more general requirement of being "capable of antagonising the Wnt signaling pathway". The latter feature was hence redundant.

Sufficiency of disclosure (Article 83 EPC)

Claim 1

The disclosure in the patent could not be insufficient for failing to disclose the percentage of inhibition of the signalling activity induced by the different Wnt ligands that qualified as an inhibition of Wnt3- and Wnt3a-specific signalling. This objection concerned an alleged lack of clarity concerning the claim's scope, but this did not prevent the skilled person from putting the claimed invention into practice.

Since the molecules were defined as monoclonal antibodies or antigen-binding fragments thereof which bound to the propeller 3 domain of LRP6 defined by a specific amino acid sequence, the claim concerned a well-known class of molecules having a characteristic structure and binding to a defined target. A structure-activity relationship also existed. Hence, the skilled person did not have to test arbitrarily selected chemical substances by trial and error, and claim 1 was not a "reach-through" claim.

To put the claimed invention into practice, the skilled person had to obtain monoclonal antibodies binding to the propeller 3 domain of LRP6 by routine methods and

screen these antibodies for their inhibition of Wnt3- and Wnt3a-specific signalling activity. This could be routinely performed using known assays, identified for example in paragraphs [0142] to [0146] and Example 1 of the patent. Hence, both steps were mere routine, lay within the capabilities of the skilled person and did not constitute an undue burden.

It was only necessary to screen for inhibition of Wnt3- and Wnt3a-induced signalling activity, since an antibody binding to the propeller 3 domain was either a Wnt agonist or a Wnt3- and Wnt3a-specific antagonist (paragraph [0180] of the patent). The Wnt3- and Wnt3a-specific inhibition thus followed from binding to the propeller 3 domain and the detected Wnt3- and Wnt3a-antagonistic activity. It was therefore not necessary to test inhibition by any other Wnt ligands that, as disclosed in the application, bound to the propeller 1 domain. However, if desired, antibodies which showed a greater degree of inhibition of Wnt3- and Wnt3a-induced signalling activity than, for example, Wnt1-induced signalling activity could be identified by comparing the relative values of the assay's signals.

LRP6 and LRP5 propeller domain deletion constructs were commonly known research tools to map the binding sites of native ligands to LRP6 and LRP5, and it had already been demonstrated that the remaining propeller domains folded correctly (e.g. Figure 5A of document D11 and Figure 2A and page 4678, left-hand column, third paragraph of document D14). The data in Table III of the patent thus credibly demonstrated which propeller domain the antibodies bound to.

The appellant had not provided any evidence that obtaining the claimed antibodies was difficult or

impossible. On the contrary, post-published evidence documents D2 and D5 demonstrated that preparation of the claimed antibodies was readily achievable, and, as confirmed by one of the inventors in a declaration (document D31), of 64 anti-LRP6 antibodies that had been tested, ten, i.e. 15.6%, were found to inhibit Wnt3- and Wnt3a-specific signalling activity by at least 75%. The claimed antibodies could therefore be obtained by routine methods without undue burden.

Claim 9

It was plausible from the application that antibodies which inhibited Wnt3 and Wnt3a signalling activity could be used for treating cancer. The link between aberrant Wnt signalling and the development of cancer was well established in the prior art. No evidence was provided for the allegation that a possible agonistic effect on Wnt1 signalling for some antibodies would counteract the antagonistic effect on Wnt3 and Wnt3a signalling such that the antibody could no longer be used to treat cancer. Post-published document D2 demonstrated that treatment of cancer with the claimed antibodies was possible. Moreover, since the patent disclosed the ability of the claimed binding molecules to agonise Wnt1 signalling when they were presented in a bivalent format, the skilled person was informed of this effect and could avoid it where necessary.

Novelty (Article 54 EPC) - claim 1

Documents D6 and D7 did not disclose any individualised monoclonal antibody or scFv which bound to the propeller 3 domain of LRP6. The disclosure of a polyclonal antibody did not implicitly disclose monoclonal antibodies (e.g. decision T 601/05,

Reasons 6.1). Nor had the appellant demonstrated that any of the LRP6 antibodies that would be produced when following the teaching in paragraphs [0433] and [0439] to [0442] of document D6 (or paragraphs [0405] to [0408] in document D7) would inevitably antagonise the Wnt signalling pathway and inhibit Wnt3- and Wnt3a-specific signalling activity. However, the burden of proof for this allegation lay with the appellant which had raised the objection. Since the evidence on file showed that LRP6 antibodies binding to the propeller 3 domain of LRP6 were not always antagonistic towards Wnt3- and Wnt3a-specific signalling activity but could also be agonists, inhibiting Wnt3- and Wnt3a-specific signalling activity was not an inherent feature of any antibody binding to the propeller 3 domain of LRP6.

An inhibitory effect on Wnt3- and Wnt3a-specific signalling activity was not an unusual parameter, since this property was assessed for other LRP6 antibodies in the state of the art, as evident for example from document D8.

The monoclonal antibody disclosed in document D8 was generated by immunisation with a synthetic peptide having an amino acid sequence that was present within the propeller 2 but not the propeller 3 domain of LRP6. Since the propeller 3 domain did not contain an identical peptide, it could not be established beyond reasonable doubt that the antibody of document D8 bound to the propeller 3 domain of LRP6.

Inventive step (Article 56 EPC)

Document D8 constituted the closest prior art. Documents D6 and D7 neither disclosed nor taught towards an antibody that was directed to the same

purpose or effect as the claimed antibodies and, as such, were not appropriate choices for the closest prior art. The claimed antibody or antigen-binding fragment thereof differed from the antibody disclosed in document D8 in that it bound to an epitope within the propeller 3 domain of LRP6. The technical effect of the difference was a preferential inhibition of Wnt3- and Wnt3a-specific signalling activity over other Wnt signalling pathways. The objective technical problem was the provision of an LRP6 antagonising antibody that preferentially inhibited Wnt3- and Wnt3a-specific signalling activity over other Wnt signalling pathways.

The patent provided sufficient evidence that this problem was solved by the claimed subject-matter (Tables II and III and paragraph [0180] and [0181] of the patent). No substantiated statements to the contrary had been presented by the appellant. The fact that the objective technical problem was solved by the claimed subject-matter was also confirmed by post-published evidence (as shown in the cross-competition and the domain-mapping experiments on pages 15474 and 15475 of document D2).

The solution provided in claim 1 was not obvious to the skilled person, because prior to the discovery that different Wnt ligands effected their signalling activity through distinct propeller domains, Wnt ligands were thought to bind to the propeller 1 and propeller 2 regions of LRP6 (e.g. documents D11 and D14). The skilled person seeking to provide an LRP6-antagonising antibody that inhibited Wnt3- and Wnt3a-specific signalling did not therefore have any incentive to consider LRP6 antibodies binding to the propeller 3 domain. Moreover, in view of the teaching in document D8, LRP6 antibodies binding to the

propeller 2 domain would have been the most likely candidates for antibodies that inhibited Wnt3- and Wnt3a-induced signalling activity. Thus, the claimed subject-matter was not obvious to the skilled person, and it involved an inventive step.

XI. The parties' requests were as follows.

The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed and that the patent be maintained on the basis of the set of claims of the main request, submitted with the reply to the appeal as auxiliary request 1, or alternatively on the basis of the set of claims of one of auxiliary requests 1 and 2, submitted with the reply to the grounds of appeal as auxiliary requests 2 and 3, and that documents D40 and D41 not be admitted.

Reasons for the Decision

Appellant not represented at the oral proceedings

1. As announced previously, the appellant was not represented at the oral proceedings (see section VII. above). In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the oral proceedings were continued in the absence of the appellant, which was considered to be relying only on its written case.

Consideration of documents D40 and D41 in appeal (Article 12 RPBA)

2. A party's appeal case should be directed to the requests, facts, objections, arguments and evidence on

which the decision under appeal was based (Article 12(2) RPBA). Under Article 12(4) RPBA, any part of a party's appeal case which does not meet the requirements in Article 12(2) RPBA is to be regarded as an amendment, unless the party demonstrates that this part was admissibly raised and maintained in the proceedings leading to the decision under appeal.

3. The opposition division's decision was not based on documents D40 and D41, which had been submitted only two weeks before the oral proceedings in opposition. This is evident from the second paragraph on page 3 of the decision under appeal, where it is stated that "*said documents [which included D40 and D41] were not referred to during the oral proceedings and did not play any role in the decisions taken by the OD*".
4. On appeal, neither the appellant nor former opponents 1 submitted any arguments as to why the opposition division might have erred in not taking the disclosure in documents D40 and D41 into account in its decision, or why documents D40 and D41 should be considered in the appeal proceedings. Hence, no justification was submitted for relying on documents D40 and D41 in the appeal proceedings. In the absence of any justification as required under Article 12(4) RPBA, the board decided not to consider documents D40 and D41 in the appeal proceedings (Article 12(4) RPBA).

Main request

Amendments (Article 76(1) EPC and Article 123(2) EPC)

Claim 1

5. Paragraphs [001] to [00239] of the descriptions of the application and the earlier application are identical, and the subject-matter of claims 1, 4 and 17 of the

application is identical to or is encompassed in the subject-matter of claims 4, 7 and 20 of the earlier application. Hence, in the following, reference will only be made to passages in the earlier application.

Claims 1, 4, 7 and 20 of the earlier application read as follows:

"1. A low-density-lipoprotein receptor-related protein 6 polypeptide (LRP6) binding molecule comprising an antigen binding portion of an antibody that specifically binds to LRP6, wherein the antigen binding portion binds to an epitope of human LRP6 (SEQ ID NO:1) within or overlapping one of the following:

- (a) amino acids 20-326 of SEQ ID NO:1;
- (b) amino acids 286-324 of SEQ ID NO:1;
- (c) amino acids 631-932 of SEQ ID NO:1; or
- (d) amino acids 889-929 of SEQ ID NO:1.

4. The LRP6 binding molecule of claim 1, comprising an antigen binding portion of an antibody that specifically binds to LRP6, wherein the antigen binding portion binds to an epitope of human LRP6 (SEQ ID NO:1) within or overlapping one of the following:

- (a) amino acids 631-932 of SEQ ID NO:1; or
- (b) amino acids 889-929 of SEQ ID NO:1.

7. The LRP6 binding molecule of any of claims 1-5, wherein the antigen binding portion is capable of antagonizing the Wnt signaling pathway.

20. The LRP6 binding molecule of any of the preceding claims, wherein the antigen binding portion is an antigen binding portion of a monoclonal antibody."

6. Claims 4, 7 and 20 of the earlier application thus disclose a low-density-lipoprotein receptor-related protein 6 polypeptide (LRP6) binding molecule comprising an antigen binding portion of a monoclonal antibody that specifically binds to LRP6, wherein the antigen binding portion binds to an epitope of human LRP6 (SEQ ID NO:1) within or overlapping amino acids 631-932 of SEQ ID NO:1 or amino acids 889-929 of SEQ ID NO:1 and is capable of antagonising the Wnt signalling pathway.

7. By comparison with this disclosure, the claimed subject-matter is amended in that the LRP6 binding molecule is further defined as follows (see section VII. for a full text of the claim).

(1) It is a monoclonal antibody or an antigen binding portion thereof (and not a binding molecule comprising an antigen binding portion of a monoclonal antibody),

(2) it binds to an epitope within amino acids 631-932 of SEQ ID NO:1 (and not to an epitope within or overlapping amino acids 631-932 of SEQ ID NO:1 or amino acids 889-929 of SEQ ID NO:1), and

(3) it inhibits Wnt3- and Wnt3a-specific signalling activity.

Amendment (1)

8. Paragraph [0010] of the earlier application discloses that LRP6 binding molecules include "*antibodies that bind to LRP6 ... such to the first or third propellers*"; paragraph [0027] of the earlier application discloses that the LRP6 binding molecule includes *inter alia* "*complete antibodies*". Therefore,

the earlier application contains a general teaching that any of the LRP6 binding molecules disclosed in the earlier application can be (complete) antibodies. Paragraph [0193] of the earlier application also refers to the LRP6 binding molecules of the invention as being "*e.g., monoclonal antibodies, or antigen-binding portion(s) thereof*", and paragraph [0083] of the earlier application defines the term "antibody" as referring to an "*intact antibody or an antigen binding fragment (i.e., 'antigen-binding portion') or single chain ... thereof*".

9. The earlier application therefore contains multiple passages that disclose in a general manner that an LRP6 binding molecule as described in the earlier application can be a (monoclonal) antibody or an antigen-binding portion thereof. From these passages, the skilled person understands that this general teaching applies to any LRP6 binding molecules described in the earlier application, including those stated in the claims to be an antigen-binding fragment of a monoclonal antibody binding to human LRP6. Amendment 1 does not therefore present the skilled person with any new technical information and hence does not add matter.

Amendment (2)

10. The definition of the antigen-binding portion of the claimed LRP6-binding molecule as binding to an epitope of human LRP6 within amino acids 631 to 932 of SEQ ID NO:1 (amendment (2) as defined in point 7. above) has a basis in option (a) of claim 4 of the earlier application. Claim 4 of the earlier application discloses that the antigen-binding portion of the LRP6 binding molecule binds to an epitope of human LRP6

within or overlapping (a) amino acids 631 to 932 of SEQ ID NO:1 and (b) amino acids 889 to 929 of SEQ ID NO:1 (see point 5. above). Selecting option (a) and then, within option (a), deleting the phrase "or overlapping" neither amounts to the selection of independent embodiments from two separate lists nor singles out a new embodiment not disclosed in the earlier application as filed. The appellant's argument that selections from two independent lists of separate embodiments were required to arrive at amendment (2) is therefore not persuasive.

Amendment (3)

11. Paragraph [0013] of the earlier application discloses that the propeller 3 domain of human LRP6 corresponds to amino acids 631 to 932 of SEQ ID NO:1. The link between binding to the propeller 3 domain of LRP6 and inhibition of Wnt3- and Wnt3a-specific signalling (amendment (3) as defined in point 7. above) is for example disclosed in paragraphs [0034], [00235] and [00236] of the earlier application.

12. Paragraph [0034] discloses that *"an antagonizing LRP6 binding molecule (e.g., which binds within the third propeller of LRP6) can inhibit, attenuate, or prevent Wnt pathway activation and signaling by, e.g., DKK1, and Wnt ligands such as as Wnt3 and Wnt3a"*. Paragraph [00235] discloses that *"Wn[t]3a-specific LRP6 antagonistic antibodies ... bind to propeller 3"*. Paragraph [00236] discloses that *"Fabs binding to propeller 3 of LRP6 function with Wnt3A specificity"* and that *"Wnt3- and Wnt3a-specific signaling activity can be most effectively inhibited by a Wnt3a specific LRP6 antagonizing binding molecule"*.

13. Thus, in particular paragraphs [00235] and [00236], which summarise the results of Example 3 of the earlier application in a generalised manner, disclose a link between binding to the propeller 3 domain and the inhibition of Wnt3- and Wnt3a-specific signalling activity. In view of this teaching, the board cannot accept the appellant's argument, raised in the context of the disclosure in paragraph [0034], that the earlier application lacked a pointer to the combination of features of binding to an epitope within the propeller 3 domain and inhibiting Wnt3- and Wnt3a-specific signalling activity.
14. Claim 1 does not contain subject-matter that extends beyond the content of the earlier application or the application as originally filed. The requirements of Article 76(1) EPC and Article 123(2) EPC are met.

Claim construction - claim 1

15. Claim 1 relates to a monoclonal antibody or an antigen-binding fragment thereof characterised by the following functional features.
- (1) It specifically binds to human low-density-lipoprotein receptor-related protein 6 polypeptide (LRP6) having the amino acid sequence of SEQ ID NO:1, wherein the antigen-binding portion binds to an epitope of human LRP6 within amino acids 631-932 of SEQ ID NO:1,
- (2) it is capable of antagonising the Wnt signalling pathway, and
- (3) it inhibits Wnt3- and Wnt3a-specific signalling activity.

16. Since claim 1 is identical to granted claim 1, it is not open to review for clarity under Article 84 EPC. Hence, the delimitations of the claimed subject-matter resulting from functional feature (3) have to be ascertained by way of interpretation. The opposition division interpreted feature (3) such that the claimed antibody or antigen-binding fragment thereof inhibited, to an undefined degree, the signalling via Wnt3 and Wnt3a, but was not required to be a specific antagonist of Wnt3 and Wnt3a and could therefore also inhibit the signalling activity by other Wnt ligands.

17. However, this claim construction does not take into account the term "specific" used in this phrase. An LRP6 antibody or antigen-binding fragment thereof that inhibits Wnt3- and Wnt3a-specific signalling activity is understood by the skilled person, in view of the common meaning of the term "specific", as inhibiting the signalling activity initiated by Wnt3 and Wnt3a to a significantly higher degree than that initiated by other Wnt ligands.

18. This interpretation is also in line with the teaching in Examples 1 to 3 of the application, where it is disclosed that anti-LRP6 antagonistic Fabs "*preferentially inhibit Wnt1- or Wnt3a-induced Wnt signaling*" (see paragraph [00231]) and that "*Wnt3- and Wnt3a-specific signaling activity can be most effectively inhibited by a Wnt3a specific LRP6 antagonizing binding molecule*" (see paragraph [00236]). This assessment is further supported by the data in Table II, according to which LRP6-binding Fabs that inhibit Wnt3- and Wnt3a-induced signalling activity may also inhibit the signalling activity by other Wnt ligands, albeit to a much lesser extent.

19. Considering the common meaning of the term "specific", feature (3) excludes the possibility that the signalling activity induced by other Wnt ligands is inhibited to a similar or the same degree as that induced by Wnt3 and Wnt3a, but does not require that the signalling activity induced by other Wnt ligands is not inhibited at all. Exclusive inhibition of the Wnt3 and Wnt3a signalling activity alone would go against scientific knowledge and is not supported by the application.

20. The appellant also argued that the expression "capable of antagonizing the Wnt signalling pathway" (feature (2) as defined in point 15. above) was a feature independent of the inhibition of Wnt3- and Wnt3a-specific signalling activity and required a net antagonistic effect of the claimed LRP6 antibody on the Wnt signalling pathway, i.e. irrespective of any other Wnt ligand that might be present in a cell.

21. The board does not accept this interpretation of the claim, because the actual wording of the claim does not require a net inhibitory effect on Wnt signalling, and a claim should be interpreted in its broadest possible technically meaningful manner. An LRP6 antibody that inhibits Wnt3- and Wnt3a-specific signalling activity is, by virtue of this property, also capable of antagonising the Wnt signalling pathway, since Wnt3 or Wnt3a ligands activate the Wnt signalling pathway. The board therefore concurs with the respondent that feature (2) as defined in point 15. above is redundant.

22. In conclusion, the claim concerns a monoclonal antibody or an antigen-binding fragment thereof that specifically binds to an epitope of human LRP6 within amino acids 631-932 of SEQ ID NO:1 and preferentially inhibits Wnt3- and Wnt3a-induced signalling activity compared to the signalling activity induced by other Wnt ligands.

Sufficiency of disclosure (Article 83 EPC)

Claim 1

23. Article 83 EPC requires the application to disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. With respect to the invention as defined in claim 1, this means that the skilled person must be able to prepare the claimed monoclonal antibody. This antibody is essentially defined by two functional features, namely that it binds to an epitope of human LRP6 within amino acids 631 to 932 of SEQ ID NO:1 and that it inhibits Wnt3- and Wnt3a-specific signalling activity, i.e. it must preferentially inhibit Wnt3- and Wnt3a-induced signalling activity over the signalling activity induced by any other Wnt ligands (see claim construction in points 15. to 22. above).
24. The preparation of a monoclonal antibody that binds to an epitope within a defined amino acid sequence, i.e. a known target, for example by immunisation of an animal with a protein or peptide consisting of or contained within the defined amino acid sequence, or by phage display using such a peptide, is a routine task for the skilled person and does not require any inventive activity. This was not contested by the appellant. Nor did the appellant contest that assays to determine an antibody's ability to influence a Wnt ligand's

signalling activity in a standardised manner were known in the art, such as the luciferase-based read-out system referred to in Example 1 of the application (see paragraph [00231]) and the LEF-1 reporter system used in document D8 (see Figure 4B and the paragraph bridging the right- and the left-hand columns of page 5979).

25. However, the appellant argued that the screening of candidate LRP6 propeller 3-binding monoclonal antibodies for their ability to antagonise the Wnt signalling pathway by inhibiting Wnt3- and Wnt3a-specific signalling activity was an undue burden.
26. In a first line of argument, the appellant asserted that, since the application did not disclose a single reproducible example, screening would have to be performed without a positive control. Only two compounds, designated "Fab002" and "Fab004", were disclosed that allegedly had the recited functional properties; however, the patent did not disclose any structural information on these compounds, or which epitope they bound to. It was not even clear whether these compounds bound to the propeller 3 domain of LRP6 at all.
27. This argument does not persuade the board. It is true that the patent does not disclose a reproducible example and comprises no figures, and that Table III does not refer to an identifier of the tested Fab fragments and therefore cannot be linked to Table II. However, Article 83 EPC does not require an application to contain a reproducible example. The lack thereof is not therefore in itself a reason to conclude that the claimed invention is not sufficiently disclosed.

28. Nor is the board persuaded that a positive control is required to test an antibody's ability to inhibit Wnt3- and Wnt3a-induced signalling activity in one of the known standard assays, since the inhibitory effect of a candidate antibody can be assessed by comparison with the effect of a non-inhibitory control antibody. A positive control would therefore only serve as a general assay control, which is not necessarily required and could be performed with any known Wnt3 or Wnt3a signalling inhibitor.

29. The appellant also raised doubts in respect of the binding of the compounds Fab002 and Fab004 to the propeller 3 domain, since this assumption was only based on the observed loss of binding of these compounds to propeller 3 domain deletion constructs. In these constructs, epitopes in the remaining propeller domains might have been lost due to structural changes in these domains. The board is not persuaded by this argument, however, as LRP6 and LRP5 propeller domain deletion proteins have already been constructed in the art and have been used to map the binding sites of native ligands to LRP6 (see for example Figure 5a of document D11 and Figure 2A and page 4679, left-hand column, third paragraph of document D14). It was therefore already known in the art that the remaining LRP6 propeller domains in propeller domain deletion constructs folded correctly. The data in Table III of the patent therefore demonstrates to which propeller domain the analysed compounds bound.

30. The appellant also referred to the different numbering of the LRP6's amino acid sequence in Figure 4A of the priority document, compared to the numbering used in the application to define the propeller 3. However, as explained by the respondent, the differences in amino

acid numbering arose from whether the LRP6's signal peptide was accounted for or not. This argument is therefore not persuasive either.

31. In a second line of argument, the appellant asserted that, since the application did not disclose a selection rule or threshold level to define what levels of inhibition of the Wnt signalling pathway by particular Wnt ligands qualified as inhibition of "Wnt3- and Wnt3a-specific signaling activity", this feature was so ill-defined that it could not be reproduced without undue burden.
32. However, this argument concerns an absence of definition of the boundaries of the claim. The determination of the boundaries of a claim is a matter of clarity of the claim (Article 84 EPC) rather than sufficiency of disclosure (Article 83 EPC). However, failure to fulfil Article 84 EPC is not a ground for opposition under Article 100 EPC. The fact that the definition of the boundaries of the claim is unclear does not as such result in an inability to reproduce the claimed antibody, as long as the application provides the skilled person with sufficient information for them to produce antibodies falling within the scope of the claim, irrespective of the claim's unclear boundaries.
33. In this context, the appellant also asserted, in a third line of argument, that since no link existed between the two functional characteristics of the claimed antibody, every antibody that bound to the propeller 3 region of LRP6 had to be screened for Wnt3- and Wnt3a-specific inhibition, a task that amounted to a research project based solely on trial and error, which constituted an undue burden.

34. However, this line of argument is not persuasive either. The claim concerns a well-defined class of molecules, namely monoclonal antibodies binding to the propeller 3 domain of LRP6. As assessed above (see point 24.), the provision of monoclonal antibodies binding to the propeller 3 domain of human LRP6 is routine for the skilled person. Methods for screening these antibodies for inhibition of Wnt3- and Wnt3a-specific signalling activity are also commonly known (see point 24.). The application and the skilled person's common general knowledge thus provide sufficient information for the skilled person to produce monoclonal antibodies that specifically bind to an epitope of human LRP6 within the propeller 3 domain and to screen these antibodies for an antagonistic activity against Wnt3 and Wnt3a.
35. The application also teaches that LRP6 antibodies binding to the propeller 3 domain are either antagonistic and inhibit Wnt3- and Wnt3a-specific signalling activity or are agonistic, that both properties are identified by the same screening method, and that Wnt1-specific LRP6 antibodies bind to the propeller 1 domain (see Examples 1, 2 and 3, in particular paragraphs [00235] and [00236] and Tables II and III of the application). According to this teaching, the two functional definitions of the antibody (binding to the propeller 3 domain and inhibition of Wnt3- and Wnt3a-specific signalling activity) are not entirely unrelated. It is therefore not necessary to test each candidate antibody for inhibition of the signalling activity induced by each of the known Wnt ligands; rather, it is sufficient to identify LRP6 propeller 3 domain-binding antibodies that antagonise Wnt3- and Wnt3a-induced signalling

(i.e. are not Wnt agonists) to obtain Wnt3- and Wnt3a-specific inhibitors. The appellant has not submitted any evidence that this teaching was incorrect.

36. Consequently, the tools for identifying antibodies having the characteristics recited in the claims are well known and only require routine steps. It may be tedious to screen candidate antibodies binding to the propeller 3 domain of LRP6 for inhibition of Wnt3- and Wnt3a-specific signalling activity, but this does not necessarily amount to an undue burden if the screening results in the desired product, i.e. if the information in the patent leads the skilled person "*directly towards success through the evaluation of initial failures*" (see decision T 544/12; Reasons 4.8). The appellant has not submitted any persuasive arguments or evidence that there were any particular difficulties to identify antibodies having the recited characteristics by the known screening assays discussed above.
37. The situation underlying the present case is not comparable with that underlying decision T 544/12, where there was evidence on file that only very few materials within an almost infinite number of organic ligands had the claimed effect, and no structure-activity relationship was present (see points 4.3, 4.5.1, 4.7 and 7.4 of the Reasons). The appellant's arguments that the claim was a reach-through claim and that the required screening processes amounted to an unreasonable task by trial and error to identify suitable antagonistic LRP6 antibodies are therefore not persuasive.
38. The appellant also argued that, since at most a single compound (Fab004) that had the desired properties had been identified in the application, the claimed

subject-matter did not correspond to the technical contribution of the application. A generalisation to antibodies only defined by two functional features was not justified, especially as no link had been established between binding to the propeller 3 domain and preferential inhibition of Wnt3- and Wnt3a-induced signalling activity.

39. However, the board does not agree that only a single non-reproducible Fab supports the finding that a preferential inhibition of Wnt3- and Wnt3a-induced signalling activity can be achieved by antibodies binding to the propeller 3 domain of LRP6. The application teaches more generally that two classes of antagonistic LRP6-binding antibodies exist, namely those that bind to the propeller 3 domain of LRP6 and inhibit Wnt3- and Wnt3a-specific signalling activity and those that bind to the propeller 1 domain of LRP6 and inhibit Wnt1-, Wnt2-, Wnt6-, Wnt7A-, Wnt7B-, Wnt9-, Wnt10A- and Wnt10B-specific signalling activity (see Examples 1 and 3 and Tables II and III of the patent). The reciprocal effect of LRP6 antibodies binding to either the propeller 1 or the propeller 3 domain on Wnt3-/Wnt3a- and Wnt1-induced signalling activity also supports the notion that propeller 3 domain-binding LRP6 antibodies that inhibit Wnt3- and Wnt3a-induced signalling activity do so preferentially over Wnt1-induced signalling activity.
40. The scant number of exemplary Fabs disclosed in the application, the lack of disclosure of the sequences of these exemplary Fabs, the lack of a direct link between Tables II and III of the application and the missing figures are hence not in themselves sufficient to call into question the general teaching in the application that the Wnt ligands fall into two groups which are

preferentially antagonised by LRP6 antibodies binding to different propeller regions of LRP6, a teaching which is incidentally supported by post-published documents D2 and D5. Therefore, this argument does not persuade the board either.

Claim 9

41. Claim 9 relates to the monoclonal antibody or antibody fragment thereof of claims 1 to 7 or the pharmaceutical composition of claim 8 for use in treating cancer (see section VII. for the full wording of the claim). The appellant did not deny that a link between aberrant Wnt signalling and the development of cancer was well established in the prior art, nor that antibodies that antagonised Wnt-induced signalling activity might be useful in the treatment of cancer. However, since the claimed antibodies, if they were in a particular bivalent IgG format, were not capable of antagonising the Wnt signalling pathway if Wnt ligands other than Wnt3 and Wnt3a were present in a cancer cell, they could not be used to treat cancer.

42. This argument is not persuasive. The known involvement of Wnt3- and Wnt3a-induced signalling activity in cancer is sufficient support for the skilled person to consider that cancer could be treated with an agent that antagonises this activity. Moreover, post-published document D2 demonstrates that a Wnt3a-dependent cancer can be treated with a bivalent IgG Wnt3a-antagonistic LRP6 antibody (see Figure 5C of document D2). The reasons submitted by the appellant are thus not sufficient to demonstrate that the claimed invention was not sufficiently disclosed.

43. In view of the above considerations, the requirements of Article 83 EPC are met.

Novelty (Article 54 EPC) - claim 1

Document D6

44. Document D6 discloses the use of 17 LRP5-specific peptides for screening a phage display library to identify single-chain variable fragments (scFvs) binding to LRP5 (see paragraphs [0439] to [0442]). It indicates in paragraph [0440] that "*[s]imilar peptides can be chosen for LRP6, ... to screen for scFv molecules*". Two of the LRP5-specific peptides are defined by amino acids 781 to 801 and 921 to 941 of the LRP5 sequence, which correspond to amino acids 768 to 788 and 908 to 928 of LRP6 and are hence contained within the propeller 3 domain of LRP6 (see Table 12 of document D6).
45. Document D6 therefore proposes identifying scFvs binding to two different peptides within the propeller 3 domain of LRP6; however, it does not disclose that any of them inhibit Wnt3- and Wnt3a-specific signalling activity. The inhibition of Wnt3- and Wnt3a-specific signalling activity is not an inherent property of scFvs binding to the propeller 3 domain-derived peptides recited in Table 12 of document D6, since antibodies binding to the propeller 3 domain of LRP6 could also be Wnt agonists (see paragraph [00236] of the application). Therefore, document D6 does not disclose an scFv that specifically binds to the propeller 3 domain of human LRP6 and inhibits Wnt3- and Wnt3a-specific signalling activity.
46. The appellant argued that the burden of proof to demonstrate that the scFvs proposed in document D6 did

not inhibit Wnt3- and Wnt3a-specific signalling activity lay with the respondent, because the claimed antibodies were only defined by functional features. It had hence to be assumed that the scFvs of document D6 that had one of the functional features (binding to an epitope within the propeller 3 domain of LRP6) also had the other functional feature. This argument is not persuasive, however, for the simple reason that, as discussed in point 45. above, the two functional properties recited in the claim are not directly linked. The burden of proof that any of the LRP6-specific scFvs obtainable by following the instruction in document D6 inhibited Wnt3- and Wnt3a-specific signalling activity lay with the appellant which had raised the objection of lack of novelty and argued that the scFvs had the required inhibitory properties.

47. The fact that the LRP6 peptides described in document D6 overlap to some extent with some of the preferred peptides identified within the propeller 3 domain in paragraph [0013] and [0014] of the application is also irrelevant, because an scFv that bound to any of these peptides might, according to the teaching in the application, likewise be a Wnt agonist.
48. The appellant also pointed to the disclosure in paragraph [0433] of document D6, where a peptide from the propeller 3 domain of LRP6 (amino acids 888 to 902; see Table 11) was used for generating a polyclonal antibody. However, the disclosure of a polyclonal antibody does not amount to the disclosure of a monoclonal LRP6 antibody by virtue of being a mixture of multiple individual monoclonal antibodies, as alleged by the appellant. The term "polyclonal antibody", as is well known to the skilled person, refers to a mixture of different, non-individualised

antibodies, with different properties such as binding affinity and specificity, while the term "monoclonal antibody" implies that only antibody molecules with the same characteristics are present. This is consistent with, for example, decision T 601/05 of 18 October 2007, point 6.1 of the Reasons, in which the board concluded that the term "monoclonal antibody" implied a certain degree of purity and specificity not present in a polyclonal antibody serum. The disclosure in paragraph [0433] and Table 11 of document D6 is not therefore prejudicial to the novelty of the claimed subject-matter solely for this reason.

49. In addition, the board does not agree with the appellant's argument that a Wnt3- and Wnt3a-specific inhibition is an unusual parameter that could not be expected to have been tested in the prior art. As discussed above (see point 24.), several assays to test a substance's influence on the Wnt signalling pathway were commercially available and had been used in the prior art to test whether antibodies bound to particular propeller regions of LRP6 (see for example document D8). This feature is accordingly neither an unusual parameter nor difficult to test for. This argument is therefore not persuasive either.
50. In view of these considerations, the disclosure in document D6 is not prejudicial to the novelty of claim 1 (Article 54 EPC).

Document D7

51. The disclosure in paragraphs [0404] to [0407] and the table on page 61 of document D7 is similar to that in paragraphs [0433], [0439] to [0442] and Table 12 of document D6. Like document D6, document D7 does not

disclose a monoclonal antibody or fragment thereof that binds to the propeller 3 domain of LRP6 and inhibits Wnt3- and Wnt3a-specific signalling activity.

Document D7 is therefore not prejudicial to the claimed subject-matter, at least for the reason presented in points 44. to 50. above in the context of the disclosure in document D6 (Article 54 EPC).

Document D8

52. Document D8 discloses a monoclonal antibody raised against a peptide (DTGTDRIEVTR) from the propeller 2 domain of LRP6. This antibody inhibits Wnt3a-induced signalling activity (see the last paragraph of left-hand column and first paragraph of right-hand column of page 5979 and Figures 4A and 4B of document D8). The appellant argued that since the propeller 2 peptide used for immunisation differed only in three amino acids from a peptide present within the propeller 3 domain of LRP6, it was highly likely that this antibody also bound to the propeller 3 domain of LRP6, and that the burden of proof lay with the appellant to prove that this was not the case.

53. This line of argument is not persuasive, however. As acknowledged by the appellant, the LRP6 propeller 3 domain does not contain a peptide identical to that used for immunisation in document D8, and document D8 does not teach that the disclosed antibody binds to the propeller 3 domain of LRP6. The peptide within the propeller 3 domain differs in three out of 11 amino acids from the peptide used for immunisation, i.e. in more than 27% of the amino acid sequence. In view of this significant difference, the board does not agree with the appellant that it was more likely than not that the antibody of document D8 would also bind to the

propeller 3 domain of LRP6. Under these circumstances, the burden of proof for the allegation that this was nonetheless the case lay with the appellant which had raised the objection. Since the appellant did not provide any evidence that the antibody of document D8 did indeed bind specifically to the propeller 3 domain of LRP6, the subject-matter of claim 1 is novel over the antibody disclosed in document D8 (Article 54 (EPC)).

Inventive step (Article 56 EPC)

Closest prior art

54. The appellant considered that document D8 and documents D6 or D7 were equally suitable as "closest prior art".

Document D8 as closest prior art

55. Document D8 discloses a monoclonal antibody that binds to the propeller 2 domain of LRP6 and inhibits Wnt3a-induced signalling activity (see point 52. above). The claimed antibody differs from this in that it binds to an epitope within amino acids 631 to 932 of SEQ ID NO:1, i.e. to an epitope within the propeller 3 domain of LRP6. Moreover, document D8 is silent on whether or not the inhibition of Wnt3a-induced signalling that it discloses is Wnt3- and Wnt3a-specific, as required for the claimed antibody. The objective technical problem can therefore be formulated as the provision of an antagonistic LRP6 antibody that preferentially inhibits Wnt3 and Wnt3a signalling activity over signalling activity induced by other Wnt ligands (see the board's claim construction in points 15. to 22. above).

56. Nothing in the prior art pointed the skilled person towards an antibody that bound to an epitope within the propeller 3 domain of LRP6 as a solution to this technical problem. Indeed, it was not known in the art that different Wnt ligands bound to different propeller domains of LRP6, and that therefore antibodies that preferentially inhibited the signalling activity induced by particular Wnt ligands could be prepared by targeting different LRP6 propeller domains. The link between binding to the propeller 3 domain of LRP6 and preferential inhibition of Wnt3 and Wnt3a signalling activity was therefore not suggested in the prior art and hence was not obvious to the skilled person.
57. The appellant argued that the skilled person starting from the disclosure in document D8 would simply screen for other Wnt3- or Wnt3a-inhibitory LRP6 antibodies, and that this screening would lead them directly to the claimed antibody. It was irrelevant that this screening would probably also result in antibodies binding outside of the propeller 3 domain of LRP6 because, in the absence of any technical effect, no motivation to select specific alternative LRP6 antibodies was required.
58. However, these arguments are based on the opposition division's claim construction that the claimed antibody was not required to preferentially inhibit Wnt3- and Wnt3a-induced signalling activity over the signalling activity induced by other Wnt ligands, on the allegation that in view of this claim construction no technical effect was associated with the claimed antibody over that disclosed in document D8, and on the consequent formulation of the objective technical problem as merely the provision of an alternative LRP6 antibody. Since the board adopted a different claim

construction (see points 15. to 22. above), these arguments are not relevant to the assessment of inventive step of the claimed antibody vis-à-vis the disclosure in document D8.

59. The appellant also referred to the fact that the Wnt antagonist Dkk1 binds to the propeller 3 domain of LRP6 (see for example the right-hand column on page 323 of document D11), and that Wnt signalling was thus also controlled by a mechanism that involved binding to this LRP6 domain. However, the fact that Dkk1 binds to the LRP6 propeller 3 domain does not make it possible to draw any conclusions on the LRP6 binding site of different Wnt ligands, since an antagonist does not necessarily exert its function by directly preventing ligand binding. Indeed, a different mechanism has been proposed in the prior art for Dkk1's antagonistic activity on Wnt signalling, namely inducing the internalisation of LRP5/6 (see for example Figure 5 and the second full paragraph on page 675 of document D9). Moreover, document D11 (right-hand column, paragraph on page 323) discloses that Wnt binds to the propeller 1 and 2 domains of LRP6.
60. Hence, it was not obvious to the skilled person, solely from the fact that Dkk1 binds to the LRP6 propeller 3 domain, that an LRP6 antibody that bound to the propeller 3 domain would inhibit Wnt3- and Wnt3a-specific signalling activity. This line of argument is therefore not persuasive. No other arguments that took the preferential inhibition of the Wnt3- and Wnt3a-induced signalling activity by the claimed antibodies into account were submitted by the appellant. Hence, the claimed subject-matter involves an inventive step over the antibody disclosed in document D8.

Document D6 and D7 as closest prior art

61. As discussed above in the context of novelty (see points 44. to 51.), documents D6 and D7 do not disclose any individual antibodies which bind to the propeller 3 domain of LRP6, and they are not concerned with an inhibitory effect on Wnt3- and Wnt3a-specific signalling activity. As correctly pointed out by the opposition division in the decision under appeal, these documents had the aim of preparing LRP5- and LRP6-binding antibodies that could "*serve as HBM mimetics, for example by displacing Dkk binding and thereby could be used as an osteoporosis therapeutic*" (see paragraph [0437] of document D6). These documents therefore intended to provide antibodies that antagonised Dkk. Since Dkk is an antagonist of Wnt signalling, these documents neither teach antibodies that have an inhibitory effect on Wnt3- and Wnt3a-specific signalling activity nor provide any incentive to search for such antibodies. Therefore, the disclosure in D6 and D7 is less suitable as a starting point for the discussion of inventive step than document D8's disclosure.
62. The appellant argued that either no motivation to provide antibodies that inhibited Wnt3- and Wnt3a-specific signalling activity was required in documents D6 or D7, since the objective technical problem was to provide such antibodies, or that there was a motivation given the common general knowledge of the role of the Wnt signalling pathway in cancer.
63. However, while the role of the Wnt pathway in cancer may have generally motivated the skilled person to screen for LRP6 antibodies that antagonised the Wnt signalling pathway, the skilled person would not have

started this screening from LRP6 antibodies that were thought to antagonise the Wnt antagonist Dkk1, and would not have screened such antibodies for an inhibitory effect on Wnt3- and Wnt3a-specific signalling activity. The appellant's arguments with respect to the teaching in documents D6 or D7 as "closest prior art" are hence based on hindsight, and are not persuasive.

64. In view of the above considerations, the appellant's arguments on inventive step are not persuasive.

65. In their statement of grounds of appeal, former opponents 1 also submitted problem-solution approaches starting from the common general knowledge on the role of Wnt3 in cancer and from the disclosure in any of documents D9, D10, D11, D15 and D17. The appellant did not rely on any of these objections, so there is no need to consider their merit. However, for sake of completeness, the board notes the following: each of these problem-solution approaches is based on the opposition division's claim interpretation that the claimed antibody only had to be capable of "*an undefined level of Wnt3/3a inhibition, without any specificity whatsoever*" (see the second paragraph on page 37 of former opponents 1's statement of grounds of appeal). Since the board does not agree with this claim interpretation (see points 15. to 22. and point 58. above), former opponents 1's assessment of inventive step in this manner is not relevant to the decision.

66. The claimed subject-matter involves an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the opposition division with the order to maintain the patent with claims 1 to 9 of the main request, filed as auxiliary request 1 with the reply to the appeal, and a description possibly to be adapted thereto.

The Registrar:

The Chair:



B. Brückner

T. Sommerfeld

Decision electronically authenticated