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Datasheet for the decision of 11 May 2021

Case Number: T 1911/17 - 3.3.04

Application Number: 08786803.0

Publication Number: 2170940

IPC: C07K14/58, G01N33/74, G01N33/68

Language of the proceedings: EN

Title of invention:
New BNP(1-32) epitope and antibodies directed against said epitope

Patent Proprietor:
Bio-Rad Europe GmbH
Centre National de la Recherche Scientifique (C.N.R.S.)

Opponent:
Grund, Dr., Martin

Headword:
BNP(1-32) epitope specific antibodies/BIORAD

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 84, 56

Keyword:

Admittance - Late-filed document - submitted with the statement of grounds of appeal (yes)
Clarity - claim 7 - main request & auxiliary request 1 (no)
Clarity - claim 2 - auxiliary request 2 (no)
Inventive step - claim 2 - auxiliary requests 3 and 4 (no) - obvious alternative

Decisions cited:

G 0003/14, T 0301/95, T 0097/00, T 0735/00, T 0187/04, T 1210/05, T 1608/13, T 0511/14, T 0605/14

Catchword:

Europäisches Patentamt
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Case Number: T 1911/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 May 2021

Appellant: (Patent Proprietor 1)	Bio-Rad Europe GmbH Holbeinstrasse 75 4051 Basel (CH)
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Appellant: (Opponent)	Grund, Dr., Martin Nikolaistr. 15 80802 Munich (DE)
Representative:	Grund, Martin Grund Intellectual Property Group Patentanwalt und Solicitor PartG mbB Postfach 44 05 16 80754 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 28 June 2017 concerning maintenance of the European Patent No. 2170940 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	O. Lechner
	L. Bühler

Summary of Facts and Submissions

I. Both the patent proprietors (appellants I; hereinafter "patent proprietors" or "proprietors") and the opponent (appellant II; hereinafter "opponent") filed appeals against the opposition division's interlocutory decision to maintain European patent No. 2 170 940 (the "patent") in amended form. The patent is entitled "*New BNP(1-32) epitope and antibodies directed against said epitope*".

II. The patent was opposed on the grounds in Article 100(a) EPC in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), as well as on the grounds in Article 100(b) and (c) EPC.

III. In the decision under appeal the opposition division decided *inter alia* that claim 1 of the main request and of auxiliary request 1 lacked novelty and that auxiliary request 2 complied with the requirements of the EPC.

IV. With their statement of grounds of appeal, the proprietors filed a main request (corresponding to auxiliary request 1 dealt with in the decision under appeal), an auxiliary request 1 (corresponding to the main request except for amendments in claims 1 and 17), an auxiliary request 2 (corresponding to the request considered allowable in the decision under appeal) and an auxiliary request 3 (corresponding to auxiliary request 8 filed during the opposition proceedings except for an amendment in claim 7).

With their reply to the opponent's appeal the proprietors filed an auxiliary request 4 (corresponding to auxiliary request 3 filed during the opposition proceedings except for an amendment in claim 2).

V. With its statement of grounds of appeal, the opponent submitted *inter alia* arguments in relation to Articles 84 and 56 EPC together with nine documents (numbered D33 to D41).

The opponent's reply to the proprietors' statement of grounds of appeal included two further documents (numbered D42 and D43).

VI. The board issued a communication pursuant to Article 15(1) RPBA and provided its preliminary opinion on some of the relevant issues.

VII. In reply, the opponent filed arguments addressing the board's preliminary opinion.

VIII. Oral proceedings took place as scheduled. The proprietors were absent, as indicated by a letter beforehand.

At the end of the oral proceedings, the chair announced the board's decision.

IX. Claim 7 of the main request and auxiliary request 1 and claim 2 of auxiliary request 2 read as follows:

"Ligand specific of an epitope of the sequence FGRKMDR, selected from the group constituted by an antibody or a fragment of said antibody which recognises the epitope, and an aptamer,

wherein the fragment of said antibody which recognises the epitope is selected from the group consisting of scFv, Fab, Fab', $F(ab')_2$ and camelids single chain antibodies,

wherein said ligand is unable to bind a sequence of amino acids of the BNP(1-32) and/or proBNP(1-108) sequence which does not comprise the FGRKMDR epitope in its entirety,

and wherein the residues F_{11}, K_{14} and R_{11} are essential for binding of said ligand to the FGRKMDR epitope, the substitution of one of these residues by an alanine leading to a reduction of at least 80% in the antigenicity of said epitope."

Claim 2 of auxiliary request 3 reads as follows:

"2. Ligand specific of an epitope of the sequence FGRKMDR, constituted by an antibody which specifically recognises an epitope of the sequence FGRKMDR, wherein the antibody is

(i) a monoclonal antibody produced by the hybridoma according to claim 1 or

(ii) a monoclonal antibody harbouring all the Complementary Determining Regions (CDR) of the monoclonal antibody produced by the hybridoma according to claim 1."

Claim 2 of auxiliary request 4 reads as follows:

"2. Ligand specific of an epitope of the sequence FGRKMDR, constituted by an antibody which specifically recognises an epitope of the sequence FGRKMDR, wherein

the antibody is a monoclonal antibody produced by the hybridoma according to claim 1".

X. The following documents are referred to in this decision:

D1 Sefarian K. R. et al., Clinical Chemistry (2007), volume 53(5), pages 866 to 873

D6 Tamm N. N. et al., Clinical Chemistry (2008), volume 54(9), pages 1511 to 1518

D11 Experimental data filed by the opponent with its notice of opposition

D28 Experimental data filed by the patent proprietors with their reply to the notice of opposition

D32 Experimental data filed by the opponent in response to the opposition division's summons

D33 Declaration of Alexander G. Semenov, PhD, filed by the opponent with its statement of grounds of appeal

XI. The arguments submitted in writing by appellants I-patent proprietors, as far as relevant for the present decision, may be summarised as follows:

Admittance of document D33

The patent proprietors' remark that it was not certain that the antibody 24C5 of the company HyTest disclosed in document D1 was the same as the antibody 24C5 disclosed and experimentally used in post-published

documents D9, D10, D11 and D32 had been known to the opponent as early as with the patent proprietors' response to the notice of opposition. Since the opponent had been in contact with the company HyTest from the very beginning of the opposition proceedings, there was no justification for not filing declaration D33 until the statement of grounds of appeal. Hence, declaration D33 had to be considered late-filed and should be disregarded.

M*ain request and auxiliary request 1 - claim 7; auxiliary request 2 - claim 2*

Clarity (Article 84 EPC)

Claim 7 of the main request (and the equivalent claims in the two auxiliary requests) defined a **"[l]igand specific of an epitope of the sequence FGRKMDR"** wherein **"said ligand is unable to bind a sequence** of amino acids of BNP(1-32) and/or proBNP(1-108) sequence **which does not comprise the FGRKMDR epitope in its entirety"** and wherein **"the residues F_{11}, K_{14} and R_{17} are essential to the binding of said ligand to the FGRKMDR epitope"** (emphasis by the patent proprietors).

There was no contradiction between (i) being unable to bind a sequence of amino acids which did "not comprise the FGRKMDR epitope in its entirety" and (ii) residues F_{11}, K_{14} and R_{11} being essential for the ligand to bind to the FGRKMDR epitope.

It was clear from the patent specification that what was meant by the inability to bind to the "FGRKMDR epitope in its entirety" was that the ligand of the invention was unable to bind to a sequence that bore a truncated form of the FGRKMDR epitope. In this respect,

paragraph [0032] of the patent specified that "***[a]lso,*** *an in-depth study on the 20G7 antibody has shown that* ***it recognises the $F_{11}GRKMDR_{17}$ (SEQ ID NO: 51)*** *epitope,* ***but does not recognise*** *the $A_{11}GRKMDR_{17}$ (SEQ ID NO: 62) sequence* ***nor the $GRKMDR_{17}I_{18}$ (SEQ ID NO: 52) sequence, nor the $C_{10}F_{11}GRKMD$ (SEQ ID NO: 50) sequence***".

Feature (ii), i.e. whereby residues F_{11}, K_{14} and R_{17} were essential for binding, provided a further limitation of the claimed ligand's binding properties, namely its binding to the three specific amino acids.

Auxiliary requests 3 and 4 - claim 2

Inventive step (Article 56 EPC)

Claim 2 of auxiliary requests 3 and 4 encompassed the BNP-binding antibody 20G7 as an embodiment.

Closest prior art

Document D1 represented the closest prior art and disclosed the BNP-binding antibody 24C5.

Difference and its effect

Antibodies 20G7 and 24C5 differed on account of both their structure and the epitope to which they bound.

Whereas antibody 20G7 bound specifically to the amino acid sequence FGRKMDR of BNP, the epitope-specificity of the antibody 24C5 was not known at the priority date of the patent.

As demonstrated by examples 7, 8 and 10 in the patent, as well as by the results in post-published document

D28, the binding properties of antibody 20G7 were superior to those of antibody 24C5.

Example 7 of the patent showed that antibody 20G7 exhibited an excellent association constant (ka) and a low dissociation constant (kd), allowing it to be characterised by an excellent affinity constant of 0.17 nM, both for BNP(1-32) and proBNP(1-108).

Examples 8 and 10 of the patent showed that the antibody linearly detected both BNP(1-32) and proBNP(1-108) at antibody concentrations ranging from 20 pg/ml to 10 000 pg/ml.

The results in document D28 confirmed that antibody 20G7 displayed better reactivity towards BNP(1-32) than the antibody 24C5 when no capture antibody was used.

Examples 13 to 15 of the patent demonstrated that the antibody 20G7 detected BNP(1-32) and proBNP(1-108) in complex blood samples.

Problem to be solved

The technical problem was providing ligands capable of specifically binding to the epitope of sequence FGRKMDR.

Obviousness

The skilled person had not been prompted to design ligands specific to the epitope of sequence FGRKMDR (i.e. BNP(11-17)) merely because it was not known to be an epitope eligible for antibody binding. It had also not been known that this epitope had the unexpected advantage of not being cleaved by neprilysin – one of

the proteases that cleaved BNP in samples. This enabled a more reliable estimation of the content of BNP(1-32) in samples.

At the priority date the antibody 24C5 commercialised in 2007 by the company HyTest was known to be specific for the BNP(11-22) epitope and not for the BNP(11-17) epitope. The earliest document cited by the opponent to show the latter binding for antibody 24C5 was document D9, but D9 was published long after the priority date of the patent.

Even if it were accepted that it was an inherent property of the antibody 24C5 to bind to the BNP(11-17)-FGRKMDR epitope, this property was unknown at the relevant date of the patent in suit, so the skilled person could not have taken it into account when attempting to solve the problem they had set out to solve.

XII. The arguments submitted by appellant II (opponent), as far as relevant for the present decision, may be summarised as follows:

Admittance of document D33

Document D33 was filed in response to the patent proprietors' concerns (mentioned for the first time during the oral proceedings before the opposition division) that the antibody 24C5 available in 2007 (and used in the experiments of documents D1, D11 and D32) and the one available in 2010 were allegedly not the same. The document was highly relevant since it showed that the antibody 24C5 disclosed in document D1 was functionally identical to the antibody used in the experiments in documents D11 and D32.

Main request and auxiliary request 1 - claim 7; auxiliary request 2 - claim 2

Clarity (Article 84 EPC)

On the one hand, the feature "said ligand is unable to bind a sequence of amino acids of the BNP(1-32) and/or proBNP(1-108) sequence which does not comprise the FGRKMDR epitope in its entirety" in claim 7 of the main request and auxiliary request 1 and in claim 2 of auxiliary request 2 was explicit to the effect that the epitope was present in its entirety in order to be bound by the claimed ligand. According to this feature, therefore, all amino acids of the epitope FGRKMDR were essential for binding.

This interpretation was backed up by paragraph [0045] of the patent, from which the skilled person unambiguously understood that an FGRKMDR epitope with amino acid deletions or substitutions was not considered to be an epitope comprising the FGRKMDR epitope in its entirety.

On the other hand, the feature "and wherein the residues F_{11}, K_{14} and R_{17} are essential for binding of said ligand to the FGRKMDR epitope" meant that only certain amino acids of the epitope FGRKMDR, namely those at positions F_{11}, K_{14} and R_{17}, were essential for binding. Consequently, according to this definition, the other amino acids were not essential for binding.

Hence, one feature taught that all seven amino acids of the epitope were essential for binding whereas the other taught that only three of them were.

Consequently, claim 1 was internally inconsistent and thus lacked clarity.

Auxiliary requests 3 and 4 - claim 2

Inventive step (Article 56 EPC)

Embodiment (i) of claim 2 was the antibody generated by the hybridoma of claim 1. The patent referred to this antibody as antibody 20G7.

Closest prior art

The antibody 24C5 disclosed in document D1 represented the closest prior art.

Difference and its technical effect

Documents D11 and D32 showed that both antibody 24C5 and antibody 20G7 bound to the FGRKMDR epitope only if said epitope was present in its entirety. Hence, both antibodies bound to the same epitope in the same manner. Furthermore, document D9 (technical notes from the company HyTest) disclosed that the antibody 24C5 did bind to the BNP(11-17) fragment.

Consequently, the only difference between antibodies 24C5 and 20G7 was their structure.

As to the effect of this difference, the proprietors argued, on the basis of examples 7, 8 and 10 of the patent and the post-published data in document D28, that antibody 20G7 was superior to antibody 24C5.

However, documents D1 (Figure 1A), D4 (Figures 27A and B) and D5 (Figures 9A and B), and

post-published documents D6 (Figure 2), D11 (Figures 1 to 3) and D32 (Figures 1 to 4) all provided evidence that the antibody 24C5 was effective in detecting both BNP(1-32) and proBNP(1-108) and that it bound to the same BNP(11-17) epitope as antibody 20G7. Figure 1 of document D32 also showed that the two antibodies had similar inhibition curves (according to these data antibody 24C5 actually performed even better).

The data provided in document D28 were of limited value because, for example, it was not indicated how the experiments were performed in detail.

Lastly, antibody 24C5 had been commercialised and routinely used for years for the very purpose of detecting BNP in samples.

Consequently, the burden to prove that antibody 20G7 performed better than antibody 24C5 was now with the patent proprietors given that the evidence referred to by them - the patent and document D28 - was not persuasive.

Problem to be solved

The technical problem was thus to be defined as providing an alternative antibody binding to BNP(1-32).

Obviousness

Using routine methods to provide an alternative antibody against a known target for which antibodies already existed did not involve an inventive step.

The parties' requests

XIII. The appellants-proprietors had requested in writing that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or of auxiliary requests 1 to 3, all filed with the statement of grounds of appeal, or, alternatively, on the basis of the claims of auxiliary request 4, filed on 28 February 2018. They furthermore requested that documents D33 to D41 be held inadmissible.

The appellant-opponent requested that the decision under appeal be set aside, that European patent No. 2 170 940 be revoked and, furthermore, that auxiliary requests 1 and 4 not be admitted into the proceedings.

Reasons for the Decision

Admissibility of the appeals

1. Both appeals comply with the requirements of Articles 106 to 108 and Rule 99 EPC and are admissible.

Admittance of document D33 (Article 12(4) RPBA 2007)

2. Document D33 was filed with appellant II's (opponent) statement of grounds of appeal. Appellants I (proprietors) requested that the document be disregarded.

3. Article 12(4) RPBA 2007 stipulates that everything presented by the parties with the statement of grounds of appeal or the reply is to be taken into account by the board if and to the extent it relates to the case

under appeal and meets the requirements of Article 12(2) RPBA 2007. Yet Article 12(4) RPBA 2007 further provides that, of those materials, the board may hold inadmissible those "*facts, evidence or requests which could have been presented or were not admitted in the first instance proceedings*".

4. The opponent argued that document D33 was filed in response to an argument not made by the proprietors until the oral proceedings before the opposition division. Therefore, filing document D33 with the statement of grounds of appeal was the earliest point in time when the document could have been filed. The proprietors argued that the argument had been known to the opponent since the proprietors' reply to the notice of opposition and should thus have been filed earlier.

5. In the context of inventive step, the discussion of the data in the patent on BNP(1-32) detection by the antibody 24C5 and the discussion of the opponent's data disclosed in document D11, it was noted in passing in the proprietors' reply to the notice of opposition that "*these discrepancies could also be due to a difference in the 24C5 antibody commercialized by HyTest in 2007 (described in D1) and used by the Patentee at that time, and the 24C5 antibody used 8 years later by the Opponent to perform the experiments of D11*" (see page 12, third paragraph). In response, the opponent did not comment on this allegation, relying instead on the experimental data in pre-published documents D1, D3 to D5 (allegedly confirmed by documents D6, D9, and D11) to disprove the data in the patent in suit, and commented on the data presented by the proprietors in document D28. In the further course of the written proceedings, neither the opposition division nor the proprietors addressed the argument that the antibody

24C5 might have been different. It was only at the hearing before the opposition division that the argument resurfaced in the context of the novelty of the subject-matter of the main request over the disclosure in document D1. The proprietors' statement is recorded in the minutes as follows: "[...] *it must be that the 24C5 antibody available in 2007 and the one available in 2010, are indeed different antibodies*".

6. Given these circumstances the board considers that there was no reason why the opponent should have filed document D33 in the opposition proceedings. Consequently, the board decided to take document D33 into account.

Main request, auxiliary request 1 - claim 7; auxiliary request 2 - claim 2

Clarity (Article 84 EPC)

7. Claim 7 of the main request and claim 2 of each of auxiliary requests 1 and 2 derive from a combination of independent claim 9 as granted with (i) the feature of dependent claim 10 as granted ("wherein said ligand is unable to bind a sequence of amino acids of the BNP(1-32) and/or proBNP(1-108) sequence which does not comprise the FGRKMDR epitope in its entirety") and (ii) the feature "and wherein the residues F_{11}, K_{14} and R_{17} are essential for binding of said ligand to the FGRKMDR" from the description page 10, lines 19 to 20 of the application as filed.

In view of decision G 3/14 of the Enlarged Board of Appeal, this type of amendment is one where it is appropriate to examine compliance with Article 84 EPC

(see also Case Law of the Boards of Appeal, 9th edition, 2019; II.A.1.4 and IV.C.5.2.2).

8. The opponent argued that the claims lacked clarity because the meaning of the ligand-characterising features (i) "unable to bind a sequence of amino acids of the BNP(1-32) and/or proBNP(1-108) sequence which does not comprise the FGRKMDR epitope in its entirety", and (ii) "wherein the residues F_{11}, K_{14} and R_{11} are essential for binding of said ligand to the FGRKMDR epitope" was inconsistent.

9. On the one hand, the feature "said ligand is unable to bind a sequence of amino acids of the BNP(1-32) and/or proBNP(1-108) sequence which does not comprise the FGRKMDR epitope in its entirety" is explicit in requiring the epitope to be present in full in order to be bound by the claimed ligand. According to this feature, each of the amino acids is thus essential for the claimed ligand to bind to the epitope FGRKMDR.

10. There was no dispute about this interpretation among the parties, who also referred to paragraphs [0032] and [0045] of the description to support it.

11. The opponent argued that the feature "and wherein the residues F_{11}, K_{14} and R_{17} are essential for binding of said ligand to the FGRKMDR epitope" would be understood to mean that only certain amino acids of the epitope FGRKMDR, namely at positions F_{11}, K_{14} and R_{17}, were essential for binding, i.e. not all amino acids of the epitope. In contrast, the proprietors submitted that the feature provided a further limitation of the binding properties of the ligand, namely that it bound to three specific amino acids within the epitope.

12. Hence, one feature teaches that all seven amino acids of the epitope are essential for binding whereas the other feature teaches that only three of them are. This inconsistency between the meaning of the two features results in a lack of clarity about the binding properties of the ligand.

13. Consequently, claim 7 of the main request and auxiliary request 1 and claim 2 of auxiliary request 2 do not comply with the requirements of Article 84 EPC.

Auxiliary requests 3 and 4 - claim 2

14. Claim 2 of both auxiliary requests 3 and 4 relates to a "monoclonal antibody produced by the hybridoma according to claim 1" (see section IX. above). It is undisputed that this is the antibody referred to as 20G7 in the patent. Inventive step is assessed below with regard to that antibody.

Inventive step (Article 56 EPC)

Closest prior art

15. The board agrees with both parties that document D1 represents a suitable springboard for assessing inventive step.

16. Document D1 discloses that peptides derived from brain natriuretic peptide (BNP) precursor (proBNP), BNP and the N-terminal fragment of proBNP (NT-proBNP) are used as biomarkers of heart failure. The anti-BNP(1-32) and anti-proBNP(1-108) antibody 24C5, generated by immunisation with the BNP(11-22) fragment, is successfully used in assays for the immunodetection of

BNP from human plasma samples. The relevant detection limits were found to be 0.4 ng/L for BNP (see abstract and results).

Difference

17. The subject-matter of claim 2 differs from the anti-BNP antibody 24C5 of document D1 in that it relates to an anti-BNP antibody named "20G7", i.e. the one produced by the hybridoma according to claim 1.

18. Both parties accepted that the two antibodies shared the feature whereby they both bind to BNP(1-32) and proBNP(1-108), and that they differed on account of their amino acid sequences, i.e. their structure.

19. There was dispute about whether a further difference resided in the epitope to which the two antibodies bind, i.e. whether or not the antibodies bind to the same epitope.

20. The proprietors did not dispute the opponent's submission, based on documents D9, D11 and D32, that, like antibody 20G7, antibody 24C5 was specific for the epitope FGRKMDR. However, they submitted that this was not known to the person skilled in the art before the priority date of the patent.

21. The epitope to which an antibody binds is an intrinsic consequence of an antibody's structure. Furthermore, it has not been argued that the epitope-specificity resulted in an effect in addition to the binding of the antibodies to BNP and proBNP. Hence, in this situation, knowing the epitope to which antibody 24C5 binds is not crucial for arriving at a proper formulation of the technical problem.

22. Consequently, the difference between the closest prior-art antibody 24C5 and the antibody 20G7 referred to in the claim is their structure.

Technical effect of the difference

23. The opponent submitted that, in view of the proprietors' position that antibody 20G7 performed better than antibody 24C5, the burden to proof this was with the proprietors.

24. The "legal burden of proof" is on the party who relies on a legal consequence arising from an alleged positive fact. Accordingly, the "legal burden of proof" is determined by the legal cases which each party presents. The "legal burden of proof" (unlike the "evidential burden of proof") does not shift (see decision T 301/95, OJ 1997, 519, point 6.2.3 of the Reasons). Whether the burden is discharged or not is assessed by the board in accordance with the appropriate standard of proof on the basis of all the evidence before it. If the party bearing the "legal burden of proof" fails to demonstrate to the required degree the fact(s) on which its legal case rests, the board has to decide against that party. There is no shift of the legal burden of proof in the appeal proceedings. Although an appellant must argue on appeal why the contested decision was wrong, this does not result in a shift of the legal burden of proof on the substance (see decisions T 1210/05, point 2.3 of the Reasons and T 1608/13, point 3.1 of the Reasons).

The legal burden of proof lies with the opponent to establish that the claimed invention lacks an inventive step. The opponent must therefore set forth the state

of the art which makes the claimed invention obvious to the person skilled in the art. If, in support of an inventive step, a patent proprietor alleges that the claimed invention has advantageous properties or effects, then the legal burden of proof for the alleged improvement over the prior art rests upon them (see decision T 97/00, point 3.1.6 of the Reasons).

25. The proprietors submitted that the improved properties of antibody 20G7 compared to antibody 24C5 were demonstrated by examples 7, 8, 10 and 13 to 15 of the patent.

26. Of those examples, only examples 8 and 10 are relevant for determining the effect of the difference because they compare both antibody 20G7 and antibody 24C5 directly.

26.1 The examples test the binding to BNP(1-32) and proBNP(1-108), respectively, of three different antibodies, including the antibodies 20G7 and 24C5, in a sandwich-ELISA format using rabbit polyclonal antibody L21016 and hinge 76 antibody, respectively, as capture antibodies.

As shown in Table 3 relating to example 8, antibody 20G7 linearly detects BNP(1-32) at concentrations ranging from 20 to 10 000 pg/ml (see also Figure 5) whereas antibody 24C5 does not.

As shown in Table 5 relating to example 10, antibody 20G7 linearly detects proBNP(1-108) at concentrations ranging from 20 to 10 000 pg/ml (see also Figure 6) whereas antibody 24C5 does not.

Comments in the patent on the results of examples 8 and 10 are that the antibody 24C5 "*behave[s] quite differently from the 20G7 antibody*", that "*20G7 is much more suitable than the 24C5*" antibody in the assay formats used, and that antibody 24C5 is "*not very effective or not at all effective in detecting BNP(1-32) and proBNP(1-108), even at high concentrations of the analyte*".

27. According to the proprietors, the results in document D28 confirmed that the antibody 20G7 displayed better reactivity towards BNP(1-32) than the antibody 24C5 when no capture antibody was used. However, since the experimental set-up in document D28 is not a sandwich-ELISA, it has not been further considered by the board (see point33. below).

28. The opponent submitted that the results of examples 8 and 10 were not suitable to demonstrate the superiority of antibody 20G7 and pointed *inter alia* to documents D1, D11 and D32. In this context, document D33 provided uncontested evidence that the antibody used in the experiments disclosed in documents D11 and D32 was the same as that used in the patent.

29. Document D1 discloses that "*[t]he antibody combination* $50E1_{26-32}$*[capture]-*$24C5_{11-22}$*[detection] manifested the highest detection limit in 1-step sandwich IFA with both synthetic and endogenous antigens ...*".

*Inter alia, d*ocument D11 discloses data (see Figure 4) from a sandwich immunoassay with BNP and proBNP using antibody 50E1 as the capture antibody and 24C5 as the detection antibody. The results show that the 24C5 antibodies "*recognize with a very good performance both BNP and proBNP (detection limit is below 0.5 pg/mL)*".

Document D32 compares the detection characteristics of antibodies 20G7 and 24C5 towards BNP(1-32) and proBNP(1-108) in a sandwich-ELISA assay using antibody 50E1 as the capture antibody. It discloses that "*[m]ab24C5 and mAb20G07 behave quite similarly*".

Hence, all three documents demonstrate that antibody 24C5 is very effective at detecting BNP(1-32) and proBNP(1-108). Moreover, document D32 shows similar detection properties for antibody 24C5 and antibody 20G7.

30. Consequently, there seems to be a contradiction between the detection characteristics of antibodies 20G7 and 24C5 disclosed in the patent and those disclosed in documents D1, D11 and D32.

31. The sandwich-ELISA assays in the patent and in documents D1, D11 and D32 were carried out with different capture antibodies. The specificity of the capture antibody determines which parts of the captured molecule are accessible for the detection antibody. Hence, the differences in the detection characteristics could be attributed to the different assay conditions.

32. As submitted by the opponent with reference to the proprietors' submissions in the opposition proceedings, the proprietors have accepted that assay conditions may influence an antibody's detection characteristics:

"*The Opponent also contradicted the statement of the Patentee according to which* 'the two commercial antibodies 24C5 and 26E2 are not very effective or not at all effective in detecting BNP(1-32), even at high concentrations of the analyte'.

We wish to point out to the Opponent that this statement was made in the context of a specific immunoassay using the ***L21016 rabbit polyclonal antibody*** *...*

As well-known from the skilled person, different results can be obtained in immunoassays using detection and capture antibodies according to the capture antibody used. This aspect is by the way confirmed in D1 which indicates that a specific antibody combination (50E1 and 24C5 antibodies) enabled obtaining a good detection of BNP (page 868, left column, §2).

The results presented in Example 5 of the patent demonstrates that, when using a different capture antibody than the 50E1 antibody such as the BioRad capture antibody L21016 antibody, the 24C5 and 26E2 antibodies are not very effective in detecting BNP(1-32). There is thus no contradiction between the results of ***D1*** *and* ***D6*** *with the 24C5 and 50E1 antibodies and the results of the Patent with the 24C5 and L21016 antibodies. They are only results obtained using different experimental conditions.*"(Emphasis in the original; see page 12, last point of the opponent's statement of grounds of appeal together with paragraph 3.4 of the proprietors' submission of 22 December 2015.)

33. On the basis of the evidence on file, the board cannot conclude that antibody 20G7 is generally superior to antibody 24C5 in detecting BNP(1-32) and proBNP(1-108).

34. Consequently, the objective technical problem is formulated as providing alternative antibodies capable of binding to both BNP(1-32) and proBNP(1-108).

Obviousness

35. In the board's view, a person skilled in the art starting from the closest prior-art antibody 24C5 would have been able to provide alternative antibodies capable of binding to BNP(1-32) and proBNP(1-108) using routine methods. Under the case law of the boards of appeal in these circumstances, the claimed subject-matter, i.e. antibodies, is obvious (see e.g. decisions T 735/00, point 26 of the Reasons; T 187/04, point 11 of the Reasons; T 511/14, points 3 and 5 of the Reasons; T 605/14, points 23, 24 and 26 of the Reasons). Therefore, the subject-matter of claim 2 does not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated