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Datasheet for the decision of 19 November 2015

Case Number: T 1329/11 - 3.3.02

Application Number: 05005356.0

Publication Number: 1577673

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:
The use of BNP-type peptides and ANP-type peptides for assessing the risk of suffering from a cardiovascular complication as a consequence of volume overload

Patent Proprietor:
F. Hoffmann-La Roche AG
Roche Diagnostics GmbH

Opponent:
B.R.A.H.M.S GmbH

Headword:
Use of BNP-type peptides/ROCHE

Relevant legal provisions:
EPC Art. 83, 133
RPBA Art. 13

Keyword:
Oral submission by accompanying person (refused)
Sufficiency of disclosure - (no)

Decisions cited:
G 0004/95

Catchword:

Europäisches Patentamt
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Case Number: T 1329/11 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 November 2015

Appellant: (Opponent)	B.R.A.H.M.S GmbH Neuendorfstrasse 25 16761 Hennigsdorf (DE)
Representative:	Simandi, Claus Patentanwalt Höhenstrasse 26 53773 Hennef / Bonn (DE)
Respondent: (Patent Proprietor 1)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Respondent: (Patent Proprietor 2)	Roche Diagnostics GmbH Sandhofer Strasse 116 68305 Mannheim (DE)
Representative:	Stolmár & Partner Patentanwälte PartG mbB Blumenstraße 17 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 April 2011 rejecting the opposition filed against European patent No. 1577673 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	U. Oswald
Members:	K. Giebeler
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 577 673, based on European patent application No. 05005356.0 and entitled "The use of BNP-type peptides and ANP-type peptides for assessing the risk of suffering from a cardiovascular complication as a consequence of volume overload", was granted with 17 claims.

II. Claim 1 as granted reads:

"A method for diagnosing the risk of a patient, who shows no symptoms of a cardiovascular disease according to the NYHA classification and who has no history of cardiovascular complication, of suffering from a cardiovascular complication as a consequence of a future increase intravasal volume, comprising the steps of
a) measuring, in vitro, the level of a natriuretic peptide from the group of ANP, or NT-proANP and/or BNP, or NT-proBNP
b) diagnosing the risk of the patient by comparing the measured level to at least one known level(s) associated with different grades of risk in a patient."

III. An opposition was filed against the granted patent on the grounds of lack of novelty and inventive step (Article 100(a) EPC) and insufficiency of disclosure (Article 100(b) EPC).

IV. The opposition division decided to reject the opposition.

V. The opponent (hereafter appellant) filed an appeal against the decision of the opposition division.

VI. With letter of 12 March 2012, the proprietors (hereafter respondents) responded to the appeal, requesting that is be dismissed; auxiliary requests I to VII as well as new documentary evidence were submitted.

Claim 1 of auxiliary request III reads:

"A method for diagnosing the risk of a patient, who shows no symptoms of a cardiovascular disease according to the NYHA classification and who has no history of a cardiovascular complication, of suffering from a cardiovascular complication as a consequence of a future increase (of) intravasal volume, comprising the steps of
a) measuring, in vitro, the level of NT-proBNP,
b) diagnosing the risk of the patient by comparing the measured level to at least one known level(s) associated with different grades of risk in a patient."

VII. On 25 March 2015, the board issued a communication as an annex to the summons to oral proceedings, expressing its preliminary view. In said communication, the board noted with respect to sufficiency of disclosure that none of the examples of the patent in suit appeared to describe that a method as defined in claim 1 as granted was carried out, and that, therefore, the question arose whether or not, at the priority date, it would have been plausible for the skilled person on the basis of the disclosure of the patent and/or common general knowledge that the claimed method would work.

VIII. Oral proceedings were held on 19 November 2015. During the oral proceedings, the respondent filed an additional request, referred to as "auxiliary request IB". Claim 1 of this request reads:

"A method for diagnosing the risk of a patient, who shows no symptoms of a cardiovascular disease according to the NYHA classification and who has no history of a cardiovascular complication, of suffering from a cardiovascular complication as a consequence of a future increase (of) intravasal volume, comprising the steps of
a) measuring, in vitro, the level of NT-proBNP,
b) diagnosing the risk of the patient by comparing the measured level to at least one known level(s) associated with different grades of risk in a patient.
[*sic*] wherein a plasma level of more than 60 and less than 1000 pg/ml of NT-proBNP in a male patient is associated with an increased risk of suffering from a cardiovascular complication, wherein said increased risk indicates that treatment may be adapted, and wherein a plasma level of more than 120 and less than 1000 pg/ml of NT-proBNP in a female patient is associated with an increased risk of suffering from a cardiovascular complication, wherein said increased risk indicates that treatment may be adapted."

IX. The following documents are mentioned in this decision:
D4: Cardiovascular Research (2001) 51: 442
D8: Anesthesiology (2009) 111: 311
D23: Experimental evidence entitled "Comparison of the diagnostic utility of BNP, NT-proBNP and NT-proANP", submitted by the respondents

X. The appellant's arguments, insofar as they are relevant for the present decision, can be summarised as follows:

The inventor, Mr Hess, should not be permitted to make oral submissions at the oral proceedings on the statistical information contained in document D23,

because this had not been specified in the respondents' letter of 21 September 2015 and thus came as a surprise to the appellant.

The claimed invention lacked sufficiency of disclosure, because none of the examples was suitable to derive a correlation between the concentration of a natriuretic peptide in a patient according to claim 1 before a treatment that resulted in an increase of the intravasal volume and the risk of said patient of suffering from a cardiovasculare complication as a result of this treatment; the claimed invention was merely based on speculation. The finding of Example 2 that volume overload resulted in elevated NT-proBNP levels was already known from the prior art (e.g. document D4) at the priority date and did not relate to a possible prognosis. Furthermore, there was no reason to assume that the apparently healthy blood donors in Example 3 that had increased NT-proBNP levels were ill. Example 4 concerned NT-proBNP levels in patients suspected of cardiac disorders and did thus not relate to patients according to claim 1. Example 8 related to patients with severe cardiac disorders, and no conclusions could be drawn from the data with respect to patients according to claim 1. Moreover, the levels measured in Example 8 were significantly higher than those in Example 3 and thus no correlation could be made.

Auxiliary request IB should not be admitted into the proceedings, because it was late-filed and did *prima facie* not overcome the objection under Article 83 EPC.

XI. The respondents' arguments, insofar as they are relevant for the present decision, can be summarised as follows:

The inventor, Mr Hess, should be permitted to make oral submissions at the oral proceedings, as requested with letter of 21 September 2015.

The invention claimed in claim 1 of the main request was sufficiently disclosed under Article 83 EPC. Although none of the examples showed a method of claim 1, the combination of Examples 2, 3, 4 and 8 demonstrated that the claimed invention could be carried out. Example 2 showed that an increase of intravasal volume resulted in increased NT-proBNP levels and thus represented a stress on the myocardium. Example 3 showed that a substantial number of apparently healthy blood donors had elevated NT-proBNP levels; these individuals could be assumed to have asymptomatic cardiac diseases and thus an increased risk of suffering from a cardiovascular complication. The patients of claim 1 included apparently healthy patients that showed only the non-obvious symptoms of NYHA classes I and II, and Example 4 showed that patients of NYHA classes I and II had elevated levels of NT-proBNP. In combination with Example 8 showing that elevated NT-proBNP levels in patients with cardiac complications indicated a risk of suffering from a cardiovascular complication as a result of a future volume overload, it could be concluded that asymptomatic individuals having elevated levels of NT-proBNP also had an increased risk of suffering from a cardiovascular complication as a result of a future volume overload.

In order to carry out the claimed method, the skilled person would simply have to carry out the teaching of Example 8 with samples of persons that had no history of a cardiovascular complication and no symptoms

according to the NYHA classification. He would then see that the invention worked. Moreover, the post-published document D8 showed that the claimed invention worked. The opponent had not provided any evidence showing that the claimed method could not be carried out.

Auxiliary request IB should be admitted into the proceedings. Its claim 1 included the features of claims 2 and 3 of the main request, which represented a limitation aiming to overcome the objection under Article 83 EPC. This subject-matter had been in the proceedings from the start.

XII. The final requests of the parties were as follows:

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

The respondents requested that the patent be maintained on the basis of the main request filed as auxiliary request III with the reply to the statement of grounds of appeal on 12 March 2012, or, alternatively, on the basis of auxiliary request Ib filed during the oral proceedings of 19 November 2015.

Reasons for the Decision

1. The appeal is admissible.

2. Admissibility of oral submissions by the accompanying person, Mr Hess, on the statistical information contained in document D23

2.1 According to decision G 4/95 (OJ EPO 1996, 412), oral submissions by an accompanying person in opposition or

opposition appeal proceedings cannot be made as a matter of right, but only with the permission of and under the discretion of the board.

When exercising this discretion the main criteria to be considered are:
i) The professional representative should request permission for such oral submissions to be made. The request should state the name and qualifications of the accompanying person, and should specify the subject-matter of the proposed oral submissions.
ii) The request should be made sufficiently in advance of the oral proceedings so that all opposing parties are able to properly prepare themselves in relation to the proposed oral submissions.
iii) A request which is made shortly before or at the oral proceedings should in the absence of exceptional circumstances be refused, unless each opposing party agrees to the making of the oral submissions requested.
iv) The EPO should be satisfied that oral submissions by an accompanying person are made under the control of the professional representative (see G 4/95 (supra), headnote and point 10 of the reasons).

2.2 At the oral proceedings, the respondents requested that Mr Hess, one of the inventors, be permitted to make oral submissions on the statistical information contained in document D23.

Document D23, which is not a published document, had been filed on 12 March 2012 by the respondents with their reply to the grounds of appeal in order to show a statistical correlation between the natriuretic peptides BNP, NT-proBNP and NT-proANP in patients with different extents of heart failure.

In their letter dated 21 September 2015, the respondents requested Mr Hess to be permitted to make oral submissions "relative to technical topics in connection with the invention underlying the patent, prior art and further medical topics which may arise during oral proceedings". Said request did thus not specify the subject-matter of the proposed oral submissions, namely the statistical information contained in document D23, in sufficient detail so as to permit the opposing party to properly prepare itself in relation to the proposed oral submissions.

It follows that criteria (i) and (ii) were not complied with, and the respondents' request that specified the subject-matter of the proposed oral submissions was only made at the oral proceedings.

In view of criterion (iii) and the appellant's request not to allow the oral submissions by Mr Hess on the statistical information contained in document D23, the respondents' request had to be refused. It is, however, also noted that the information contained in document D23 could in any case only supplement but not substitute the information in the patent in suit in the determination of sufficiency of disclosure.

Consequently, the board did not allow Mr Hess to make the requested submissions.

It is pointed out that in view of the fact that the main request now under consideration refers solely to NT-proBNP, the contents of document D23 is of no relevance with respect to the present decision (see point 3 below).

3. Main request - Sufficiency of disclosure

3.1 According to Articles 100(b) and 83 EPC, the claimed invention must be disclosed in the European patent and in the European patent application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. According to the established case law of the boards of appeal, this requirement must be complied with at the effective date.

3.2 Claim 1 is directed to a method for diagnosing the risk of a patient, who shows no symptoms of a cardiovascular disease according to the NYHA classification and who has no history of a cardiovascular complication, of suffering from a cardiovascular complication as a consequence of a future increase of intravasal volume, whereby the level of the natriuretic peptide NT-proBNP is measured in vitro and the risk of the patient is diagnosed by comparing the measured level to at least one known level(s) associated with different grades of risk in a patient.

The claimed method thus concerns diagnosing the risk of suffering from a cardiovascular complication as a consequence of a future increase of intravasal volume in a patient of a specified patient group, namely patients who show no symptoms of a cardiovascular disease according to the NYHA classification and who have no history of a cardiovascular complication.

3.3 The classification of cardiovascular diseases into the functional classification system according to the New York Heart Association (NYHA) is referred to in paragraph [0029] of the patent in suit. It is stated in said paragraph that patients of class I have no obvious

symptoms of cardiovascular disease; physical activity is not limited, and ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). Patients of class II have slight limitation of physical activity; they are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. Patients of class III show a marked limitation of physical activity; they are comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Patients of class IV are unable to carry out any physical activity without discomfort; they show symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Furthermore, paragraph [0040] of the patent in suit states with respect to the term "patient" according to the invention that "the patient has no known history of cardiovascular complication, and no (NYHA class I or II) symptoms of a cardiovascular complication".

In view of these teachings, the board considers that only those patients that do **not** show any of the symptoms set out in paragraph [0029] of the patent in suit, such as slight limitation of physical activity, or fatigue, palpitation or dyspnea resulting from ordinary physical activity, are patients according to claim 1.

The respondents' submission that because class I and II patients only showed symptoms which were not typical for a cardiac dysfunction, i.e. "non-obvious" symptoms, such patients would fall under claim 1 as long as their cardiac status (i.e. their classification into class I or II) had not been determined, cannot be followed by the board. This is because claim 1 explicitly refers to

"symptoms of a cardiovascular disease according to the NYHA classification", and not to "obvious" symptoms or to symptoms typical for a cardiac dysfunction; the respondents' reading of claim 1 would thus be contrary to both the explicit wording of claim 1 and the teaching of the description of the patent in suit, notably paragraphs [0029] and [0040].

3.4 None of the examples of the patent in suit describes that a method according to claim 1 was actually carried out, i.e. that the risk of a patient of the specified patient group of suffering from a cardiovascular complication as a consequence of a future increase of intravasal volume was diagnosed on the basis of measuring the level of NT-proBNP. This was not disputed by the respondents.

In these circumstances, it needs to be assessed whether or not, at the priority date, it would have been plausible for the skilled person on the basis of the disclosure of the patent in suit and/or common general knowledge that the claimed method would work, i.e. that the risk of a patient of the patient group specified in claim 1 of suffering from a cardiovascular complication as a consequence of a future increase of intravasal volume can be diagnosed on the basis of measuring the level of NT-proBNP.

3.5 Example 8 is the only example in the patent in suit which attempts to correlate the diagnosis of a cardiovascular complication occurring after an increase of intravasal volume to the level of NT-proBNP present before the increase of intravasal volume. It is stated that a total of 120 patients in an intensive care unit were diagnosed in regular intervals and NT-proBNP was analysed retrospectively. Five patients with a history

of cardiovascular complication, who obtained infusion therapy and/or termination of treatment with diuretics, had a subsequent clinical diagnosis of cardiac insufficiency. The example provides the data of the NT-proBNP levels of these five patients only, and not those of any of the remaining 115 patients, who did not suffer from a cardiac complication following an increase of intravasal volume. The significance of the data provided with respect to a correlation between the level of NT-proBNP and the risk of suffering from a cardiac complication following a future increase of intravasal volume is therefore rather limited. Notwithstanding this lack of statistical significance, all five patients for whom such correlation is alleged to be present had a history of cardiovascular complication, which means that none of them is a patient according to claim 1. Consequently, the data of Example 8 do not allow any conclusion as to whether or not NT-proBNP may serve as a prognostic marker for the risk of suffering from a cardiovascular complication as a consequence of a future increase of intravasal volume with respect to the patient group of claim 1.

3.6 The respondents have argued that the combination of Examples 2, 3, 4 and 8 showed that the claimed method worked.

3.6.1 Examples 2 and 3 provide data relating to apparently healthy patients who qualify as patients according to claim 1.

Example 2 concerns experiments with healthy volunteers and reports NT-proBNP levels measured **after** an increase of the intravasal volume had occurred. These data thus do not allow any conclusion with respect to the **prognostic** value of NT-proBNP in said patient group.

Example 3 concerns the determination of NT-proBNP levels in blood donors that were considered to be clinically healthy. The data obtained were used to define reference values based on the 97.5 percentile for males and females under the age of 50 years. It was observed that a substantial number of individuals had NT-proBNP levels exceeding said reference values, and that the number of such individuals increased with age.

The board cannot follow the respondents' argument that the blood donors of Example 3 with elevated NT-proBNP levels had hidden, asymptomatic cardiovascular diseases, because there is no evidence or information whatsoever to show that this was the case. The respondents' suggestion that said blood donors with elevated NT-proBNP levels had such hidden diseases and consequently had an increased risk of suffering from a cardiovascular complication, like the patients of Example 8, thus amounts to mere speculation. Such speculation cannot provide a basis for a sufficient disclosure under Article 83 EPC.

3.6.2 Example 4 concerns NT-proBNP levels in patients presenting to cardiologists with suspected cardiac disorders. The patients were classified into NYHA classes I to IV. The majority of the patients had elevated NT-proBNP levels.

The board takes the position that said patients with suspected cardiac disorders are not to be regarded as patients according to claim 1. Therefore, the data presented in Example 4, taken alone or in combination with Example 8, do not allow any conclusion with respect to diagnosing the risk of a patient as defined in claim 1 of suffering from a cardiovascular

complication as a consequence of a future increase of intravasal volume.

3.6.3 Consequently, Examples 2, 3, 4 and 8, taken alone or in combination, cannot make it plausible that the claimed method works.

3.7 The respondents have furthermore submitted that in order to perform the claimed invention, the skilled person would simply have to carry out the teachings of Example 8, but with samples of patients as defined in claim 1. He/she would then see that the invention worked.

The board cannot follow this line of argument, because in order to establish whether or not the claimed invention could be carried out, the skilled person would have to collect and evaluate additional clinical data, which would represent a research project and hence an undue burden.

3.8 The respondents have referred to post-published documents, in particular to document D8 published more than five years after the priority date, in order to show that the claimed method worked.

It is the established case law of the boards of appeal that post-published evidence may not be used to establish sufficiency of disclosure. Such evidence may only be used to backup a finding of sufficiency of disclosure.

Therefore, the contents of documents which were not available to the skilled person at the priority date cannot help to overcome the major problem of sufficiency of disclosure of the claimed invention at

the priority date, as set out in points 3.1 to 3.7 above.

3.9 The board also cannot accept the respondents' argument that the claimed invention was sufficiently disclosed because the appellant did not present verifiable facts that it did not work. Although generally, the burden of proof in the framework of sufficiency of disclosure lies with the appellant, this principle does not apply to cases like the present one, where the application as filed does not provide a single example or other technical information from which it is plausible that the claimed invention can be carried out.

3.10 In view of the above, the requirement of sufficiency of disclosure is not complied with.

Consequently, the main request must be refused pursuant to Article 83 EPC.

4. Auxiliary request IB - Admission (Article 13 RPBA)

4.1 Auxiliary request IB was filed at the oral proceedings. Its claim 1 differs from claim 1 of the main request in that it defines plasma levels of NT-proBNP which are supposed to be associated with an increased risk of suffering from a cardiovascular complication.

4.2 The board had to decide on the admission of this request. According to the established case law of the boards of appeal, claims filed at oral proceedings must *prima facie* overcome the issues raised, without giving rise to new ones, in order to be admissible.

4.3 The amendments in claim 1 introduce cut-off values for plasma NT-proBNP levels, which *prima facie* do not

overcome the fundamental deficiency under Article 83 EPC set out above for the main request.

4.4 Consequently, the board has decided not to admit the auxiliary request 1B into the proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated