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Datasheet for the decision of 23 February 2021

Case Number: T 1369/17 - 3.3.01

Application Number: 11743231.0

Publication Number: 2609427

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Language of the proceedings: EN

Title of invention:
Use of biomarkers in the assessment of the early transition from arterial hypertension to heart failure

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

Opponent:
Adams, Harvey Vaughan John

Headword:
Troponin as biomarker for heart failure/ROCHE

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 54(2), 56, 123(2)

Keyword:

Late-filed requests - admitted (yes)
Late-filed evidence
Novelty - (yes)
Inventive step - (no)
Amendments - added subject-matter (yes)

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Case Number: T 1369/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 23 February 2021

Appellant: (Patent Proprietor 1)	Roche Diagnostics GmbH Sandhofer Strasse 116 68305 Mannheim (DE)
Appellant: (Patent Proprietor 2)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
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Representative:	Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 April 2017 concerning maintenance of the European Patent No. 2609427 in amended form**

Composition of the Board:

Chairman	J. Molina de Alba
Members:	T. Sommerfeld
	L. Bühler

Summary of Facts and Submissions

I. European patent 2609427 is based on application No. 11743231.0, which was filed as an international application published as WO 2012/025355. The patent is entitled "Use of biomarkers in the assessment of the early transition from arterial hypertension to heart failure" and was granted with 15 claims.

II. Opposition was filed against the granted patent, the opponent requesting that the patent be revoked in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC), insufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. In an interlocutory decision announced at oral proceedings, the opposition division decided that the patent could be maintained in amended form on the basis of the auxiliary request filed during oral proceedings (Articles 101(3)(a) and 106(2) EPC).

The opposition division considered that the claim set according to the main request lacked novelty, namely that claim 11 lacked novelty over document D7, whereas it decided that the auxiliary request met the requirements of the EPC, in particular Articles 123(2), 54, 56 and 83.

IV. The patent proprietors and the opponent each filed appeals against the decision of the opposition division.

V. With the statement of grounds of appeal, the patent proprietors (hereinafter, appellant-patentees) requested that the decision "be set aside, as far as the Main Request filed on March 8, 2017 does not meet the requirements of Article 54(2) EPC and as far as the auxiliary requests AR1B to AR6D filed on January 9, 2017 would not fulfil the requirements of Rule 80 EPC". They moreover requested that the patent be maintained "on the basis of the following Main or Auxiliary Requests: Main Request, AR1, AR1A (corresponds to AR1 as upheld by the Opposition Division), AR1B, AR1B*, AR1C, AR1C*, AR1D, AR1D*, AR1E, AR1E*, AR2, AR2*, AR2A, AR2A*, AR2B, AR2B*, AR2C, AR2C*, AR2D, AR2D*, AR2E, AR2E*, AR2F, AR2F*, AR3, AR3*, AR3A, AR3A*, AR3B, AR3B*, AR3C, AR3C*, AR3D, AR3D*, AR3E, AR3E*, AR3F, AR3F*, AR4, AR4*, AR4A, AR4A*, AR4B, AR4B*, AR4C, AR4C*, AR5, AR5*, AR5A, AR5A*, AR5B, AR5B*, AR5C, AR5C*, AR6, AR6*, AR6A, AR6A*, AR6B, AR6B*, AR6C, AR6C*, AR6D, AR6D*". The main request and auxiliary requests AR1 and AR1A as well as all auxiliary requests with an asterisk were filed with the statement of grounds of appeal, while the remaining requests were those filed with the letter of 9 January 2017. The appellant-patentees moreover requested that documents D15 to D19 not be admitted into the proceedings.

VI. With the statement of grounds of appeal, the opponent (hereinafter, appellant-opponent) requested that the decision be set aside "to the extent that it [the opposition division] decided to maintain the patent in an amended form" and that the patent be revoked in its entirety. It also requested that none of the requests filed with the submissions of 9 January 2017 be admitted into the proceedings, and that the "second Main Request and AR1 submitted for the first time during the oral proceedings on 8 March 2017 should not

be admitted into the appeal proceedings". It moreover requested that documents D15 to D19 submitted with a letter of 6 January 2017, and new documents D20 to D35 and declaration E1, all submitted with the grounds of appeal, be admitted into the proceedings.

VII. With the letter of reply to the patentees' statement of grounds of appeal, the appellant-opponent requested that AR1, AR1B to AR6D and AR1B* to AR6D* not be admitted into the proceedings, and submitted a new document, D36.

VIII. With the letter of reply to the opponent's statement of grounds of appeal, the appellant-patentees maintained their requests and further requested: that new documents D20 to D35 and declaration E1 not be admitted; that the appellant-opponent's submissions on sufficiency of disclosure relating to the assessment of left ventricular hypertrophy and the definition of the feature "early Stage B" not be admitted into the proceedings; and that the new submissions on inventive step based on D3 and D7 as closest prior art or which combine the closest prior art with document D31 not be admitted either. They moreover requested that the case be remitted to the department of first instance for further prosecution and apportionment of costs should the board admit any of these documents or submissions.

IX. Summonses to oral proceedings before the board were issued, followed by a communication pursuant to Article 15(1) RPBA setting out issues to be discussed at oral proceedings and providing a preliminary opinion on some of them.

X. Oral proceedings before the board took place on 23 February 2021, by videoconference with the agreement of the parties.

XI. During the oral proceedings, the appellant-patentees maintained the main request and auxiliary requests 2*, 4B* and 5B* and withdrew all other requests. At the end of the oral proceedings, the chairman announced the board's decision.

Claim 1 of the **main request** reads as follows:

"1. A method of diagnosing functional and/or structural abnormalities of the heart preceding heart failure in a subject suffering from hypertension, the method comprising the steps of:
a) measuring in a blood, serum or plasma sample obtained from the subject the concentration of cardiac Troponin T or I, and
b) diagnosing said functional and/or structural abnormalities by comparing the concentration determined in step (a) with a reference amount
wherein the subject does not show left ventricular hypertrophy, and
wherein the structural and/or functional abnormalities of the heart preceding heart failure comprise an abnormality selected from a left ventricular structural change, an increased septum diameter, an increased posterial wall diameter, and diastolic dysfunction."

Claim 1 of **auxiliary request 2*** differs from claim 1 of the main request in that the following feature (underlined) has been introduced:

"... wherein the subject does not show left ventricular hypertrophy, and wherein the subject does not suffer from renal failure, and ..."

Claim 1 of **auxiliary request 4B*** differs from claim 1 of the main request in that the following amendments have been introduced (insertions underlined, deletions struck through):

"1. A method of diagnosing an ~~functional and/or structural~~ abnormality~~ies~~ of the heart preceding heart failure, said abnormality being diastolic dysfunction, in a subject suffering from hypertension, the method comprising the steps of:
a) measuring in a blood, serum or plasma sample obtained from the subject the concentration of cardiac Troponin T or I, and
b) diagnosing said ~~functional and/or structural~~ abnormality~~ies~~ by comparing the concentration determined in step (a) with a reference amount
wherein the subject does not show left ventricular hypertrophy~~, and~~
~~wherein the structural and/or functional abnormalities of the heart preceding heart failure comprise an abnormality selected from a left ventricular structural change, an increased septum diameter, an increased posterial wall diameter, and diastolic dysfunction~~."

Claim 1 of **auxiliary request 5B*** differs from claim 1 of the main request in that the following amendments have been introduced:

"1. ...
a) measuring in a blood, serum or plasma sample obtained from the subject the concentration of cardiac Troponin T or I, ~~and~~

b) measuring in the sample the concentration of IGFBP7, and
c) diagnosing said functional and/or structural abnormalities ...
..."

XII. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D2 Sundström et al., Eur. Heart J. 30, 2009, 773-81
D7 Mallamaci et al., Amer. J. Kidney Diseases 40(1), 2002, 68-75
D31 ACC/AHA Practice Guidelines: "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult"
D36 Iliou et al., Nephrol. Dial. Transplant. 16, 2001, 1452-8

XIII. The submissions of the appellant-patentees, in so far as relevant to the present decision, may be summarised as follows:

Admission of documents D31 and D36

D31 had only been submitted during appeal and no reasons had been given as to why it could not have been filed earlier. Moreover, it was not *prima facie* relevant to the claimed subject-matter, and could not be considered evidence of common general knowledge because it was an article and not a textbook.

D36 was filed even later and was not relevant to the claimed subject-matter.

Main request, claim 1: novelty and inventive step

Claim 1 was novel over D2 since, as stated by the opposition division, it had three distinguishing features: the purpose of the method, the specific abnormalities, and the group of patients with hypertension and no left ventricular hypertrophy. Contrary to the appellant-opponent's arguments, it could not be considered that the specific abnormalities were implicit in the disclosure of subclinical myocardial damage. Moreover, D2 (page 779, left column, third paragraph, and right column, first and second paragraphs) proposed many speculative explanations for the increase of cTnI which had nothing to do with the claimed abnormalities. It was not disclosed in D2 that cTnI was increased in patients with hypertension either.

As for inventive step, D2 provided no indication of the heart abnormalities listed in the claim, so it was in fact not a realistic starting point. It listed a number of possible causes for the observed troponin I increases such as tachycardia, physical exertion, aortic stenosis, anaemia (page 779, left column to right column). Only with the knowledge of the patent, a conclusion could be drawn on the underlying abnormalities, but this was an impermissible *ex-post-facto* analysis. Moreover, patients with hypertension represented only 30% of the total cohort and there was no pointer to this population. Some of the patients might even already have had mild heart failure, as stated on page 780, left column, lines 7 to 8. Document D7 was the only document referring to some of the claimed abnormalities, but the skilled person would not have combined D2 with D7 since these documents related to completely different studies: D2 was a community-based cohort study (title) while D7 dealt with

haemodialysis patients (title). No comparison between the two studies would have been possible.

Auxiliary request 2, claim 1: inventive step*

This claim excluded patients with renal failure, and therefore its subject-matter was further removed from D7. The skilled person would definitely not have combined D2 with D7, since D7 was concerned with patients undergoing haemodialysis and there was no indication that its teachings could be applied to patients without renal failure.

Auxiliary request 4B, claim 1: added subject-matter*

This claim had its basis in the original claims 1, 3, 4 and 7, combined with page 28 first paragraph or page 76, second paragraph, and page 24, second and third paragraphs, where hypertension was disclosed individually. Hypertension was repeatedly disclosed throughout the application (original claim 4; page 1, first paragraph; page 3, penultimate paragraph; page 6, line 31; page 17, last paragraph; page 18, first paragraph, second and third bullet points; page 19, first to third paragraphs, referring also to diastolic dysfunction; page 24, line 7 and lines 20 to 21; Examples, in particular page 94, line 15), so it was clear that it was a preferred embodiment. There was no selection from multiple lists, because the features were also disclosed individually.

Auxiliary request 5B, claim 1: added subject-matter*

The basis for the amendment could be found in the original claim 10 in combination with the original claims 1 and 3. It was also found in the description on

page 29, lines 12 to 21; page 39, line 26; and page 44, last paragraph to page 46, second paragraph. There was no multiple selection because the features were disclosed individually.

XIV. The arguments of the appellant-opponent, in so far as relevant to the present decision, may be summarised as follows:

Admission of documents D31 and D36

Document D31 was cited as evidence that the abnormalities recited in the claim were known in the prior art. It represented common general knowledge and was cited in the patent, e.g. in paragraphs [0008] and [0041], so it should be well-known to the patent proprietor.

D36 was filed in response to the submission of new auxiliary request AR1, but was also relevant to the main request, because it supported the argument that the combination of documents D2 and D7 had not been made with hindsight, contrary to the conclusions of the opposition division.

Main request, claim 1: novelty and inventive step

Document D2 disclosed all the features of claim 1. Even if it did not explicitly disclose the specific abnormalities listed in the claim, it was clear from the patent (paragraph [0055]) that these were simply those abnormalities that underlay left ventricular dysfunction. The patients initially had risk factor(s) for heart failure without structural and/or functional abnormalities, and would then progress into the disease by developing such abnormalities in a continuous

process. The subclinical myocardial damage disclosed in D2 (page 773, Introduction, right column, second paragraph; page 780, Conclusions) underlay said abnormalities, so they were implicitly disclosed.

As for inventive step, D31 provided evidence of the background knowledge concerning development of heart failure. Heart failure was a progressive disorder (section 2.3 on page e160 of D31, and paragraph [0055] of the patent), in which structural and functional abnormalities of the heart developed with disease progression. As displayed in Figure 1 of D31, stage A included patients with risk factors (such as hypertension) but no heart abnormalities. Then structural abnormalities developed, causing the disease to progress to stage B. As indicated in the patent (paragraph [0057]), left ventricular failure resulted from changes in the septum and posterior wall. Both claim 1 and D2 started with patients in stage A, i.e. with risk factors but still no heart failure. The only distinguishing feature from the claimed subject-matter was that D2 did not disclose the specific heart abnormalities, and the problem could be formulated as how to diagnose the listed abnormalities by measuring cTnI or cTnT. The claimed solution was obvious from D2 in combination with common general knowledge or D7. D2 disclosed that elevated levels of cTnI indicated subclinical myocardial damage and were associated with higher risk of heart failure and with severity of disease (page 779, right column, third paragraph). Accordingly, the method of D2 could detect heart abnormalities right at the beginning of their development (paragraph [0055] of the patent, D31).

Auxiliary request 2, claim 1: inventive step*

The same arguments as for claim 1 of the main request applied to this claim too. There was no reason to doubt that D2's conclusions could be applied equally to patients without renal failure. In fact, D2 did not distinguish at all between presence or absence of renal failure.

Auxiliary request 4B, claim 1: added subject-matter*

While all the features now in claim 1 were disclosed in the application, the present combination involved a multitude of selections. Three selections from three lists had to be made: risk factor hypertension from all other possible risk factors; cardiac troponin T or I from cardiac troponin and variants thereof; and diastolic dysfunction from among the four abnormalities listed. Diastolic dysfunction was individualised in the original claim 7, but this claim depended *inter alia* on claim 6, which included the presence of increased septum diameter. As to hypertension, page 24 also listed all the other risk factors as preferred embodiments, so an arbitrary selection had to be made.

Auxiliary request 5B, claim 1: added subject-matter*

Similar arguments applied to this claim as to claim 1 of auxiliary request 4B*. The original claim 10 referred to IGFBP7, but as one of two alternatives, and the same was true for the disclosure on page 29. On page 39, IGFBP7 was disclosed in a specific context, including cut-off values that were not part of the claim. Likewise, in the examples there were further limitations (patient groups; measurement of troponin T

only; measurement of other markers) which were not in the claim. Hence the insertion of this feature into claim 1 was either a selection from a further list or represented an intermediate generalisation.

XV. The appellant-patentees requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, or alternatively on the basis of one of auxiliary requests AR2*, AR4B*, and AR5B*, all filed with the statement of grounds of appeal.

The appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. The appeals are admissible.

2. Admission of the main request and auxiliary requests 2*, 4B* and 5B*

2.1 Admission of the main request and auxiliary requests 2*, 4B* and 5B* was discussed at the oral proceedings, and the board decided to admit all of these requests into the proceedings. However, in view of the outcome of the present decision, the board sees no need to provide its reasoning for this part of the decision.

3. Admission of documents D31 and D36

3.1 Documents D31 and D36 were both submitted by the appellant-opponent, D31 with the statement of grounds

of appeal and D36 with the reply to the appellant-patentees' statement of grounds of appeal. The appellant-patentees requested that none of these documents be admitted into the proceedings.

3.2 Pursuant to Article 25(2) RPBA, Article 12(4) RPBA 2007 continues to apply to any statement of grounds of appeal filed before 1 January 2020 and any reply thereto filed in due time. This is the case for the present appeal. Article 12(4) RPBA 2007 gives the board the power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the proceedings before the examining or opposition division, or which do not meet the requirements of Article 12(2) RPBA 2007.

3.3 Document D31 was submitted in reaction to the decision of the opposition division, as evidence of common general knowledge at the effective date of the patent. Moreover, this document is cited in the patent, e.g. in paragraph [0008], as being the source reference for the classification of the heart failure stages as listed in the patent. The board disagrees with the arguments of the appellant-patentees that D31, being an article and not a textbook, does not represent common general knowledge. It is established case law that common general knowledge can be inferred from a number of different sources, and it is the publication content rather than the format that determines whether the disclosure is part of the common general knowledge or not. It is already apparent from D31's title ("ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure") that the document compiles the knowledge concerning chronic heart failure at that date (2005). The board thus considers that this document is relevant as evidence of the background

knowledge underlying the patent. Accordingly, the board decided to admit D31 into the proceedings.

3.4 As to document D36, it was used by the appellant-opponent in the context of Article 56 EPC in a line of argument starting from D7 as closest prior art. The appellant-patentees had objected to the admission of this line of argument. At oral proceedings, the board asked the parties to discuss inventive step starting from D2, and therefore considered that D36 was not to be admitted to this discussion. In view of the final outcome of the present decision, the board does not see a need to provide its reasoning for this part of the decision.

4. Main request

Claim 1, novelty over D2:

4.1 According to the appealed decision and the appellant-patentees, the disclosure of document D2 was distinct from the claimed subject-matter in that the purpose of the method was different, the group of patients was different, and the specific abnormalities to be diagnosed according to claim 1 were not disclosed in D2.

4.2 The board agrees that document D2 does not disclose, either explicitly or implicitly, any of the four abnormalities of claim 1 and that it is therefore not novelty-destroying for the subject-matter of claim 1. The board however disagrees with the appellant-patentees' arguments that a group of patients as claimed, having hypertension but no left ventricular hypertrophy, is not disclosed in D2. As argued by the appellant-opponent, all patients of D2's cohort are

free from left ventricular hypertrophy (page 774, left column, section "Study sample", lines 13 to 18), and a significant number of them (355 out of 1089: Table 1 on page 777) are on antihypertensive therapy, which fact implicitly discloses that they suffer from hypertension. Since the conclusions of D2 that troponin I is a marker for heart failure are drawn in relation to all patients of the cohort, they necessarily apply to the subgroup of patients having hypertension too.

4.3 The board thus comes to the conclusion that claim 1 of the main request is novel over document D2 (Article 54(2) EPC).

Claim 1, inventive step:

4.4 The present patent is directed to "a method of diagnosing early stages of functional and/or structural abnormalities of the heart preceding heart failure in an individual bearing risk factors of developing heart failure" (paragraph [0001]). Such risk factors are, in a preferred embodiment, hypertension and/or diabetes, and "the present invention provides a method of predicting the risk of heart failure before left ventricular hypertrophy (LVH) is apparent (i.e. visible by e.g. echocardiography or ECG)" (paragraph [0001]).

4.5 According to the patent, "An individual having functional and/or structural abnormalities of the heart preceding heart failure does not show signs of heart failure", i.e. the individual is "apparently healthy" (paragraph [0053]). The following paragraph then explains that "Heart failure often starts with a change in the geometry of the left ventricle, changing potentially both systolic and diastolic function (left ventricular dysfunction LVD)" and that "LVD may develop

into left ventricular hypertrophy (LVH) in which the walls of the ventricle thicken". It is moreover explained that "Left ventricular dysfunction begins with stress or injury to the myocardium and is generally a progressive process, resulting in a change in the geometry and structure of the LV [left ventricle]. The chamber dilates and/or hypertrophies and becomes more spherical. This process is generally referred to as cardiac remodeling" (paragraph [0055]). The patent goes on to explain that "the method of the present invention allows for diagnosing structural abnormalities of the heart preceding heart failure and/or preceding left ventricular hypertrophy" (paragraph [0056]), and finally indicates that "The diagnosis of LVH, preferably, includes measurements of the septum diameter, left ventricular posterial wall thickness and end diastolic diameter, with calculation of left ventricular mass according to formulae known in the art" (paragraph [0057]).

4.6 The disclosure of the patent summarised above, as apparent from the patent itself, is part of the background knowledge of the skilled person. It is furthermore reviewed in document D31, for example in Figure 1, which schematically depicts how the progression of the disease occurs and how its different stages are defined. It is clear that the so-called stages A and B include the group of patients as defined in claim 1, namely patients who do not yet have left ventricular hypertrophy (and who do not yet have heart failure) but have risk factors such as hypertension. While the patients in stage A do not have any structural heart changes, it is the development of said changes that determines the progression of the disease into stage B. Clearly the risk of developing overt heart failure increases when the disease progresses

from stage A to stage B, i.e. when structural changes occur in the heart. It is also apparent, as stated in section 2.3 (page e160) of D31 and in paragraph [0055] of the patent, that heart failure is a progressive disorder.

4.7 Document D2, which has been taken as the closest prior art in the appealed decision, is the report of a study on assessing risk of heart failure based on the analysis of a marker for cardiomyocyte damage (abstract) on patients without electrocardiographic (ECG) left ventricular hypertrophy (page 774, left column, section "Study sample", lines 13 and 14; page 779, left column, first paragraph). It is thus directed to a similar problem to the present patent and hence suitable as a starting point for the discussion of inventive step.

4.8 The difference from the claimed subject-matter is the purpose of the method, which is to measure risk of heart failure in D2, and not to diagnose functional and/or structural abnormalities of the heart preceding heart failure as in the claim. However, as is apparent from the patent (see above), the ultimate aim of the claimed method is in fact to predict the risk of heart failure in patients without left ventricular hypertrophy, which is exactly the same as in D2. Moreover, the definition of heart failure itself (see e.g. patent, paragraph [0080]) links this condition to "any structural or functional cardiac disorder that impairs the ability of the heart to fill with or pump a sufficient amount of blood throughout the body". Hence the technical effect associated with the differences from the closest prior art is that underlying changes in the heart are diagnosed which are predictive of heart failure in patients having hypertension but no

apparent left ventricular hypertrophy. The technical problem can thus be formulated as the provision of a method of diagnosis (or detection) of functional and/or structural abnormalities of the heart preceding heart failure in said group of patients. The solution is the method as claimed and the board is satisfied that it plausibly solves the problem. In this context, the board notes that the patent does not disclose a method that can distinguish each of the four listed abnormalities from one another, but rather a method that allows a conclusion to be drawn as to the presence of at least one such abnormality.

4.9 As argued by the appellant-opponent, document D2 discloses the use of cardiac troponins as tools for diagnosing subclinical myocardial damage and for assessing the risk of heart failure in a subject cohort that does not show left ventricular hypertrophy. Of the 1089 subjects studied, 355 were on antihypertensives (Table 1): therefore, although not explicitly stated in D2, it is implicit that these were patients with hypertension (see also above, section 4.2). Hence at least one third of the subjects studied in D2 met the two conditions required in the claim, namely that they were hypertensive and had no left ventricular hypertrophy. Document D2 then concludes that, in the studied sample, higher cTnI levels were associated with a higher risk of subsequent heart failure (page 779, first paragraph of section "Discussion"). D2 does not distinguish between patients with or without hypertension, so it can be assumed that the conclusions are valid for the whole group. Accordingly, it is irrelevant that, as argued by the appellant-patentees, there was no pointer in D2 to this particular group of patients. The skilled person would thus have derived from D2 that determination of cardiac troponin I levels

in patients with hypertension but no left ventricular hypertrophy was a method suitable for predicting risk of heart failure in said patients. It remains to be determined whether it would also have been obvious to the skilled person that such a method was suitable for detecting structural and/or functional heart abnormalities as in the claim.

4.10 As argued by the appellant-patentees, D2 is indeed silent on detection of structural and/or functional heart abnormalities, let alone those listed in the claim. As mentioned above, however, it was known that heart failure develops as a consequence of structural heart disease (e.g. paragraphs [0054] and [0067] of the patent; Figure 1 of document D31). It was apparent from Figure 1 of D31 (and also described in the patent, e.g. paragraphs [0067] to [0069]) that it is the occurrence of structural heart disease that defines the change from stage A ("at high risk for HF [heart failure] but without structural heart disease or symptoms of HF") to stage B ("structural heart disease but without signs or symptoms of HF"). Examples of patients in stage A are those patients with risk factors such as hypertension, atherosclerotic disease, diabetes, obesity, etc., while patients in stage B include those with left ventricular remodelling. The board thus holds that the skilled person would have considered that any marker that indicated a higher risk of developing heart failure in a group of patients with stage A risk factors as defined in D31 (to which by definition the patients studied in D2 belonged) also necessarily indicated ongoing structural heart changes, because these were the hallmark of progression to overt heart failure. Hence the skilled person would have interpreted an increase in cardiac troponin I as disclosed in D2 not only as indicative of a higher risk of developing heart

failure but also as an indicator that structural heart changes were taking place. The skilled person would not have known what specific structural changes were taking place but would at least have expected them to include those known to lead to left ventricular hypertrophy (which was known to be a consequence of arterial hypertension: patent, paragraph [0009]), such as increase in septum diameter and in left ventricular posterial wall thickness (patent, paragraph [0057]).

4.11 The appellant-patentees further argued that document D2 speculated on different possible mechanisms underlying increase in troponin levels, such as tachycardia, physical exertion, aortic stenosis, anaemia (page 779, left column), myocardial strain, severe cardiomyocyte injury or death, or leakage of unbound sarcoplasmic cTnI through damaged membranes (page 779, right column). The board notes however that document D2, while listing a number of possible causes of troponin increases, does come to the conclusion that the observed troponin increases were an indicator of subclinical myocardial damage and correlated with an increased risk of developing heart failure. The other possible causes of troponin increase which are not related to heart failure were listed merely as a warning that, when applying the method, the existence of such situations should be ruled out (e.g. page 780, left column, line 8: "In order to exclude...").

4.12 Hence the board comes to the conclusion that the subject-matter of claim 1 of the main request does not involve an inventive step over document D2 as closest prior art, combined with common general knowledge as represented by D31. The main request is thus not allowable for lack of compliance with Article 56 EPC.

5. Auxiliary request 2*

Claim 1, inventive step:

5.1 This claim differs from claim 1 of the main request in that the group of patients to be diagnosed is further restricted to patients that do not suffer from renal failure.

5.2 Document D2 does not explicitly state that the patients do not suffer from renal failure, but since renal failure is not listed among the conditions present in the patient cohort (Table 1) it follows that none of the patients had renal failure. Even if they had, D2 does not make any distinction between patients having or not having renal failure. Hence the same arguments as given above for claim 1 of the main request also apply to this claim.

5.3 Claim 1 of auxiliary request 2* thus also lacks inventive step, and accordingly this request is not allowable for lack of compliance with Article 56 EPC.

6. Auxiliary request 4B*

Claim 1, added subject-matter:

6.1 Claim 1 of auxiliary request 4B* reads:

"1. A method of diagnosing an abnormality of the heart preceding heart failure, said abnormality being diastolic dysfunction, in a subject suffering from hypertension, the method comprising the steps of:
a) measuring in a blood, serum or plasma sample obtained from the subject the concentration of cardiac troponin T or I, and

b) diagnosing said abnormality by comparing the concentration determined in step (a) with a reference amount
wherein the subject does not show left ventricular hypertrophy."

6.2 As the basis for this claim, the appellant-patentees indicated the originally-filed claims 1, 3, 4 and 7, as well as page 76, second paragraph, and page 24 of the application as filed.

6.3 Claims 1, 3, 4 and 7 as originally filed read:

"1. A method of diagnosing functional and/or structural abnormalities of the heart preceding heart failure in a subject suffering from hypertension, diabetes, obesity, metabolic syndrome and/or having a history of smoking, the method comprising the steps of:
a) measuring in a sample obtained from the subject the concentration of at least one cardiac troponin or a variant thereof,
b) optionally measuring in the sample the concentration of one or more other marker(s) of heart failure, and
c) diagnosing said functional and/or structural abnormalities by comparing the concentration determined in step (a) and optionally the concentration(s) determined in step (b) with a reference amount
wherein the subject does not show left ventricular hypertrophy, and
wherein the structural and/or functional abnormalities of the heart preceding heart failure comprise an abnormality selected from a left ventricular structural change, an increased septum diameter, an increased posterial wall diameter, and diastolic dysfunction."

"3. The method according to any of claims 1 to 2, wherein the cardiac troponin is troponin I or T or a variant thereof."

"4. The method according to any of claims 1 to 3, wherein the subject suffers from hypertension, in particular arterial hypertension, and/or diabetes, in particular type 2 diabetes."

"7. The method of any one of claims 1 to 6, wherein the functional and/or structural abnormality is a diastolic dysfunction, in particular diastolic dysfunction asymptomatic diastolic left ventricular dysfunction with preserved left ventricular ejection fraction (LVEF)."

6.4 On page 76, second paragraph, the term "sample" is further defined as being "a sample of body fluid", which "include[s], preferably, samples of blood, plasma, serum, urine, samples of blood, plasma or serum". The last sentence of this paragraph teaches that "Cardiac troponins or a variant thereof, NT-proBNP or a variant thereof, GDF-15 or a variant thereof and IGFBP7 or a variant thereof are, preferably, determined in a blood serum or blood plasma sample". On page 24 it is stated that the subject suffers from hypertension (e.g. first line of the second paragraph, and third paragraph).

6.5 Hence the subject-matter of claim 1 of auxiliary request 4B* can be considered disclosed in the combination of the original claim 7 (diastolic dysfunction) with one of the two alternatives of claim 4 (hypertension), with two of the three alternatives of claim 3 (cardiac troponin T or I), with the disclosure on page 76 (blood, serum, plasma samples). However,

this specific combination involves a selection from several lists: selection of diastolic dysfunction from the four abnormalities mentioned in the originally-filed claim 1 and throughout the application; selection of hypertension from the at least five alternatives ("and/or") mentioned in the originally-filed claim 1 and throughout the application; selection of cardiac troponin T and I from cardiac troponin and variant thereof mentioned in the originally-filed claim 1 and throughout the application.

6.6 Apart from the fact that diastolic dysfunction is mentioned separately in the original claim 7, there is no further teaching in the application as filed indicating that diagnosis of diastolic dysfunction, in isolation from the other abnormalities listed in claim 1 as originally filed, would be a preferred embodiment or envisaged at all. In view of the combination with claim 6, on which claim 7 depends, reading that "the functional and/or structural abnormality is an increased septum diameter", it would appear that in fact at least this structural abnormality should be present as well.

6.7 As for hypertension, this is indeed mentioned throughout the application and in particular on page 24 as one preferred embodiment, but so is diabetes. As emphasised by the appellant-patentees, the third paragraph on page 24 states that "it is also contemplated that said subject suffers from hypertension alone". This is however not presented as a preferred embodiment, but just as a further embodiment: it is given as much weight as the preceding sentence that reads "a subject bearing risk factors of heart failure may suffer from hypertension accompanied by one or more of the above-referenced further risk factors".

Moreover, the claim is not limited to a subject having only hypertension as risk factor either.

6.8 Likewise, for cardiac troponin T or I, the application repeatedly refers generally to cardiac troponin or a variant thereof (as in the original claim 1) or specifically to cardiac troponin T or I or a variant thereof (as in the original claim 3); in the examples, cardiac troponin T is assessed.

6.9 Accordingly, the board considers that, although the present combination of features is conceptually disclosed in the application as filed, this disclosure involves selecting specific elements from more than one list, without there being a clear pointer to such a combination. The board thus comes to the conclusion that the subject-matter of claim 1 of auxiliary request 4B* adds subject-matter, contrary to Article 123(2) EPC.

7. Auxiliary request 5B*

Claim 1, added subject-matter:

7.1 This claim differs from claim 1 of the main request in that a further method step has been added, namely the step "measuring in the sample the concentration of IGFBP7". As the basis for this amendment, the appellant-patentees indicated the original claim 10 as well as the passages in the application as filed on page 44, last paragraph to page 46, second paragraph; page 29, lines 12 to 21; page 39, lines 26 to 30; page 94, lines 27 to 32.

7.2 The board notes that the originally-filed claim 10 discloses IGFBP7 (or a variant thereof) as one of two

alternative further markers of heart failure. Moreover, the original claim 10 refers back to step b) of claim 1, which reads "b) optionally measuring in the sample the concentration of one or more other marker(s) of heart failure" and is followed by step c), which reads "c) diagnosing said functional and/or structural abnormalities by comparing the concentration determined in step (a) and optionally the concentration(s) determined in step (b) with a reference amount". It is apparent from claim 1 that if a further marker is to be measured, then the measured concentration should be compared to a reference amount: this is however not in the present claim 1. The passage on page 29 again refers to both markers GDF-15 and IGFBP17 (and variants thereof) as alternative further markers: it however fails to disclose the other features of the claim. The passage on page 39 refers specifically to IGFBP7 but in the context of cut-off reference amounts, which are not in the claim. The passages on pages 44 to 46 are a general disclosure of IGFBP7. Finally, the passage on page 94 is part of Example 1, which starts on page 93 with the following sentence: "Troponin T, NT-proBNP, GDF-15 and IGFBP7 were determined in the following collectives of individuals." The example then goes on to describe that "The data show that the levels of IGFBP7 are higher in subjects of group 3 (hypertensive subjects with functional and/or structural abnormalities of the heart preceding heart failure) than in group 1 (normotensive subjects) and in group 2 (only bearing risk factors of suffering from heart failure). Insulin growth factor binding protein 7 levels keep on augmenting when individuals proceed to heart failure dilated cardiomyopathy (DCM, group 4)" (page 94, lines 26 to 32); however, exactly the same observations are made in relation to GDF-15 (paragraph above). Moreover, the examples relate to

specific embodiments in which the patient groups are defined by even more criteria than what is in the claim, so they cannot provide a basis for claim 1.

7.3 Hence the board considers that claim 1 of auxiliary request 5B* adds subject-matter, contrary to Article 123(2) EPC. Auxiliary request 5B* is thus not allowable.

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:

M. Schalow J. Molina de Alba

Decision electronically authenticated