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Datasheet for the decision of 19 November 2019

Case Number: T 0319/16 - 3.3.07

Application Number: 08774183.1

Publication Number: 2170405

IPC: A61K49/04, A61K51/04, A61K49/06

Language of the proceedings: EN

Title of invention:
IMAGING DIAGNOSTICS BY COMBINING CONTRAST AGENTS

Patent Proprietor:
nanoPET Pharma GmbH

Opponents:
Siemens Aktiengesellschaft
GE Healthcare Limited
Dr. Volker Vossius Patentanwälte Partnerschaftsgesellschaft

Headword:
Imaging Diagnostics By Combining Contrast Agents / NANOPET

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

Keyword:

Oral proceedings - non-attendance of appellant/patent proprietor
Inventive step - main request, auxiliary request I (no)
Late-filed request - request withdrawn before the opposition division - submitted with the statement of grounds of appeal - admitted (no)

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Case Number: T 0319/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 November 2019

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 9 December 2015 revoking European patent No. 2170405 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman C. Schmidt
Members: E. Duval
D. Boulois

Summary of Facts and Submissions

I. European patent 2 170 405 (hereinafter "the patent") was granted on the basis of six claims.

Claim 1 as granted related to an extracellular contrast medium (hereinafter ECCM) comprising gadolinium-DTPA for use in the diagnosis of lesions, wherein the ECCM was to be used in combination with a lesion-specific contrast medium (hereinafter LSCM) selected from a list of ^{18}F-based PET tracers, and further defined regarding visualization means, LSCM concentration in the lesion, and simultaneous or delayed application of ECCM and LSCM.

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, was not patentable within the terms of Article 53(c) EPC, was not sufficiently disclosed and extended beyond the content of the application as filed.

III. The appeal was filed by the patent proprietor (appellant) against the decision of the opposition division to revoke the patent. The decision was based on a single main request filed by letter dated 5 October 2015, comprising a set of claims for Germany and a different set of claims for all other Contracting States.

Claim 1 of the main request, in its version for all Contracting States except Germany, read as follows:

> "An extracellular contrast medium (ECCM) for the use in the diagnosis of lesions, wherein the ECCM is gadolinium-DTPA (gadopentetatic acid/dimeglumine

salt), wherein the ECCM is to be used in combination with a lesion-specific contrast medium (LSCM), wherein the LSCM is a ^{18}F-based PET tracer selected from the group comprising ^{18}F-fluordesoxyglucose(FDG), ^{18}F-dopamine, ^{18}F-L-DOPA, ^{18}F-fluorcholine, ^{18}F-fluormethylethylcholin, ^{18}F-fluordihydrotestosterone and wherein the combination of ECCM and LSCM is visualized by means of polymodal synthetic imaging methods and wherein said combination is used as polymodal time-delayed application or polymodal simultaneous application and wherein the LSCM concentrates in the lesion after 10 minutes and stays there for at least one hour and wherein the ECCM and LSCM are applied at the same time or the LSCM is applied with a short time delay of 30 minutes maximum."

Claim 1 of the main request, in its version for Germany, differed from the above claim 1 for all other Contracting States by the additional feature "wherein the imaging signals are immediately interpolated".

IV. In the present decision, reference is made to the following documents:

D31: Downer, J. *Medical Solutions*, pages 76-79; March 2007 "Das Beste aus zwei Welten"
D45: Higuchi et al. *J Nucl Med.*, February 2007, 48(2), 288-294
D47: Cohade C et al. *J Nucl Med.*, 2003, 44(3), 412-416 "Initial experience with oral contrast in PET/CT: phantom and clinical studies"
D48: Antoch G et al. *J Nucl Med.*, 2002, 43(10), 1339-1342 "Focal tracer uptake: a potential artifact in contrast-enhanced dual-modality PET/CT scans"

D49: Antoch G. *J Nucl Med.*, 2004, 45(Suppl), 56S-65S "To enhance or not to enhance? ^{18}F-FDG and CT contrast agents in dual modality ^{18}F-FDG PET/CT"
D54: Magnetom Flash 3/2006, page 21-23; "BrainPET* The Next Wave in the Evolution of Medical Imaging"
D55: Lois, C. et al. *Eur J Nucl Med Mol Imaging*, 2012, 39:1756-1766 "Effect of MR contrast agents on quantitative accuracy of PET in combined whole-body PET/MRI imaging"
D56: Beyer et al. *Magnetom Flash* 3/2010 "MR/PET-Hybrid Imaging for the Next Decade"
D58: Brendle, C. et al. *Radiology* 2013, 268(1): 190-9 "Simultaneously acquired MR/PET Images compared with sequential MR/PET and PET/CT: Alignment quality"
D59: Abraham et al. *Br J Dermatol.* 2008, 158(2): 273-180, Epub 2007 Dec 7 "Dermal inorganic gadolinium concentrations: evidence for in vivo transmetallation and long-term persistence in nephrogenic systemic fibrosis"
D63: Margolis, N. E. et al. *Proc. Intl. Soc. Mag. Reson. Med.* 22 (2014): 1090
D64: Rosenkrantz, A.B. et al. *Proc. Intl. Soc. Mag. Reson. Med.* 22 (2014): 4100
D65: Rosenkrantz, A.B. et al. *Proc. Intl. Soc. Mag. Reson. Med.* 22 (2014): 0039
D68: von Schulthess, G.K. "Integrated modality imaging with PET-CT and SPECT-CT: CT issues", *Eur Radiol Suppl* (2005) 15(Suppl 4): D121-D126

V. According to the decision under appeal,

(a) The main request comprising two separate sets of claims was admitted into the proceedings.

(b) The subject-matter of the set of claims for all Contracting States except Germany complied with the

requirements of Article 123(2) EPC, it met the criteria of sufficiency of disclosure, it was not excluded from patentability by Article 53(c) EPC, it was entitled to the claimed priority date of 22 June 2007 and it was novel.

However the requirements of Article 56 EPC were not complied with. D45 represented the closest prior art. D45 did not disclose administration of the LSCM agent with a short time delay of 30 minutes maximum after the ECCM agent. This difference resulted in an enhanced specificity deriving from the simultaneous registration of the MR and PET signals. The objective technical problem was to enhance the specificity of the imaging methods disclosed in D45. The claimed solution was obvious in light of D31.

(c) The subject-matter of the set of claims for Germany also complied with the requirements of Article 123(2) EPC, of sufficiency of disclosure and of novelty, but lacked an inventive step over a combination of D45 with D31.

VI. With its statement of grounds of appeal, the appellant filed a main request and auxiliary requests I and II.

The main request was identical to the main request underlying the decision under appeal, comprising a set of claims for Germany and a different set of claims for all other Contracting States.

The claims of auxiliary request I were identical to the claims for Germany according to the main request.

Claim 1 of auxiliary request II differed from claim 1 of the main request (in its version for Germany) by the additional feature "wherein said synthetic imaging method is a PET-MRI fusion method".

VII. The Board summoned the parties to oral proceedings, and set out its preliminary opinion in a communication pursuant to Article 15(1) RPBA. According to this preliminary opinion, neither the main request nor auxiliary request I fulfilled the criteria of inventive step, and auxiliary request II was not to be admitted into the proceedings.

No substantive submissions were made in reply to this communication. All parties announced that they would not attend the scheduled oral proceedings.

The oral proceedings were cancelled.

VIII. The appellant's arguments can be summarised as follows:

The purpose of the present invention was the enhancement of specificity (i.e. the sum of true negatives divided by the sum of all people without disease) and sensitivity (i.e. the sum of true positives divided by the sum of all people with disease symptoms) of diagnosis of lesions using a polymodal synthetic imaging method and using gadolinium DTPA as ECCM and a certain ^{18}F-based PET tracer as LSCM.

D45 could not be the closest prior art because its purpose was totally different. D45 could not aim for enhancement of specificity since all rats studied had suffered a myocardial infarction. Rather, D45 pointed to the use of more specific PET tracers, thus leading away from the claimed invention. The purpose underlying

the disclosure of D45 was the quantification of the size of infarcted tissue in experimental animals.

D45 did not disclose that
- the ECCM and LSCM were applied at the same time or the LSCM was applied with a short time delay of 30 minutes maximum, and
- the combination of ECCM and LSCM was visualized by means of polymodal synthetic imagining methods.

Furthermore, in D45, a sequential PET/MR was performed, and both images were superimposed later on. There was no hint in D45 that simultaneous PET-MR may enhance specificity.

The problem to be solved was to enhance specificity of the sequential MR-PET method of D45. D63-D65 showed that this problem was solved by the subject-matter of claim 1.

There was no hint in the prior art that this effect of enhancement of specificity could be reached by the claimed method. For the following reasons, it was furthermore not obvious to use an ECCM in combination with an LSCM in the diagnosis of lesions, where the ECCM and LSCM were applied at the same time or the LSCM was applied with a short time delay of 30 minutes maximum:
- it was believed that polymodal synthetic imaging methods were sensitive enough (as shown in D54, D56, D58),
- there was a strong motivation in the art to omit MR contrast agents as there may be harmful (see D59),
- contrast agents were believed, at the priority date, to introduce a bias when used in combination (see D47-

D49). Only later was it shown (see D55) that PET and Gd-DTPA could be used simultaneously, and
- there was no advantage in combining PET with MR (following D68).

D31 showed the use of simultaneous PET/MRI to increase spatial resolution, but did not aim at increasing both sensitivity and specificity. Additionally, in D31, the BOLD imaging was performed in D31 in MRI without using any contrast agent.

IX. The appellant requests that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed by letter dated 5 October 2015, or, as an auxiliary measure, on the basis of auxiliary request I filed by letter dated 5 October 2015 or auxiliary request II filed by letter dated 22 October 2015.

X. None of the respondents (opponents) made any request in the appeal proceedings or filed any substantive response to the appellant's statement of grounds of appeal.

Reasons for the Decision

Cancellation of the oral proceedings

1. In the present appeal proceedings, only the appellant requested oral proceedings as an auxiliary measure. Oral proceedings were initially appointed as a result of the appellant's request.

By letter dated 5 November 2019, the appellant subsequently stated that it would not attend the oral

proceedings. Such a statement is normally treated as equivalent to a withdrawal of the request for oral proceedings (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, III.C. 4.3.2).

The present decision can accordingly be issued without oral proceedings taking place.

Main request, set of claims for all Contracting States except Germany

2. Inventive step

2.1 The opposition division considers that D45 represents a suitable starting point for the assessment of inventive step. The Board concurs, for the following reasons.

D45 relates to the combination of PET and MRI for imaging ischemic injury in the rat model. D45 discloses (see the abstract and the experimental protocol on page 289) a sequential PET-MRI study performed on the myocardium of normal and infarcted rats, in which Gd-DTPA MRI is followed within 24 hours by ^{18}F-FDG imaging.

The appellant contests the choice of D45 as closest prior art on the ground that D45 does not aim for enhancement of specificity, since in the experimental procedure of D45 all rats have suffered a myocardial infarction. The Board however observes that the issue of imaging specificity is explicitly mentioned in D45 (see page 288, right column) and that D45 aims at characterising not only infarcted rats but also normal rats (see title and abstract).

2.2 The claimed subject-matter differs from the teaching of D45 in that the ECCM and LSCM are applied at the same time or the LSCM is applied with a short time delay of 30 minutes maximum.

Contrary to the appellant's position, the feature "the combination of ECCM and LSCM is visualized by means of polymodal synthetic imaging methods" does not constitute a further difference over D45. Indeed, figure 3 on page 291 of D45 discloses a fusion between PET images and contrast-enhanced MRI. This sequential PET/MRI procedure followed later by a superimposition of the images qualifies as a time-delayed polymodal synthetic imaging method.

2.3 No effect is shown to result from the above differentiating feature, i.e. from the application of the LSCM at the same time as the ECCM or with a short time delay of 30 minutes maximum.

None of D63-D65 compare the specificity of a method in which the LSCM is applied at the same time or with a delay of up to 30 minutes after ECCM application with a method in which the contrast agents are applied as in the closest prior art D45.

In the decision under appeal, the opposition division infers from D63 that an enhanced specificity derives from the simultaneous registration of the MR and PET signals. However, it is not a feature of claim 1 that the MRI and PET be recorded simultaneously.

Furthermore, in the method defined in claim 1, the LSCM may be administered up to 30 minutes after the ECCM, by which time the ECCM may not be present anymore in the body of the patient as a result of its much shorter

elimination time (see paragraphs [0009] and [0024] of the specification). Consequently, it does not follow from the wording of claim 1 that the LSCM and ECCM are present at the same time in the body of the patient when the scanning is performed.

Additionally, in D63, the LSCM (FDG) was administered at least 90 minutes *before* the ECCM (Gd-DTPA), rather than up to 30 minutes *after* the ECCM as required by claim 1.

Accordingly, no effect has been shown to arise as a result of the differentiating feature over the whole scope of claim 1.

2.4 The technical problem is therefore the provision of an alternative to the method disclosed in D45.

2.5 D45 already suggests the use of integrated PET/MRI systems (see page 288, right column; page 293, left column). D31 discloses such integrated systems allowing both registrations to be carried out simultaneously, or at least in one session (see page 76, right column) and mentions the advantages thereof regarding differentiation between atrophy and lower brain activity (see page 78). As noted by the opposition division, the simultaneous PET/MRI imaging system of D31 would justify a simultaneous administration of the contrasts agents. It is in that respect not relevant that D31 is limited to BOLD imaging without contrast agent, as asserted by the appellant, because the use of the claimed combination of ECCM and LSCM is already shown in D45, and the possibility to carry out both imaging techniques in one session using one system will lead the skilled person to administer both contrast agents with a short delay. Consequently, the skilled

person is led to the claimed invention by a combination of D45 with D31.

2.6 This conclusion is not modified by the appellant's further arguments, according to which it was not obvious to use an ECCM in combination with an LSCM in the diagnosis of lesions, where the ECCM and LSCM are applied as defined in claim 1.

The appellant relied on documents D54, D56, D58 and D68 to show that the skilled person would not have expected any improvement from the claimed invention, i.e. that it was believed that polymodal synthetic imaging methods were sensitive enough, and that no advantage would have been expected from combining PET with MR. However, in the Board's view, since no advantage is shown to be achieved by the claimed invention over the closest prior art, the absence of expectation of any such advantage is not relevant.

The appellant also asserted that the skilled person would expect disadvantages from the claimed invention, namely because MR contrast agents may be harmful (see D59), and because contrast agents were believed to introduce a bias when used in combination (see D47-D49). In the Board's view, the scientific articles D47-D49 and D59 do not reflect the common general knowledge and are not suitable to demonstrate a established technical prejudice. Additionally, the combined use of the contrast agents Gd-DTPA and ^{18}F-FDG is already disclosed in the closest prior art D45, such that the alleged prejudice does not concern the differentiating feature.

In conclusion, the subject-matter of claim 1 of the main request (for all Contracting States except

Germany) does not involve an inventive step over a combination of D45 with D31.

Main request, set of claims for Germany, and Auxiliary request I

3. The main request (for Germany) and auxiliary request I are identical. Both differ from the main request (for all Contracting States except Germany) by the addition of the feature "the imaging signals are immediately interpolated" in claim 1.

4. Inventive step

4.1 Starting from the closest prior art D45, the objective technical problem remains the provision of an alternative to the imaging methods disclosed in D45.

4.2 Even though D31 does not teach immediate interpolation of the MR and PET signals, it is evident that once the MR and PET signals have been collected and saved, the fact that they are interpolated immediately or after a given time does not have any technical effect on the final result. Thus the feature pertaining to the immediate interpolation of the imaging signals represents a mere arbitrary choice from a host of possible solutions and does not confer any inventive step to the subject matter of claim 1.

4.3 Accordingly, the subject-matter of claim 1 of the main request (for Germany) and of auxiliary request I does not involve an inventive step over the combined teachings of D45 and D31.

Auxiliary request II

5. Admission into the proceedings

5.1 Together with the statement setting out the grounds of appeal, the appellant submitted an amended set of claims as auxiliary request II. This auxiliary request II had been filed during the proceedings before the opposition division by letter dated 22 October 2015, but was withdrawn during the oral proceedings before the opposition division after a negative conclusion was announced regarding the main request.

5.2 Under Article 12(4) RPBA, the boards have discretion to refuse to admit requests which could have been presented (or were not admitted) in the opposition proceedings.

5.3 According to the Boards' established case law, this applies all the more to requests that were filed and subsequently withdrawn during the opposition proceedings, since such a course of events clearly shows that these requests could have been presented in those proceedings (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, V.A. 4.11.3. f)). This applies, in the present case, to auxiliary request II.

Moreover, the withdrawal of auxiliary request II prevented the opposition division from giving a reasoned decision thereon, which means the Board would be compelled either to give a first ruling on this issue or to remit the case to the opposition division if this request were admitted.

Accordingly, auxiliary request II is not admitted pursuant to Article 12(4) RPBA.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos C. Schmidt

Decision electronically authenticated