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Datasheet for the decision of 20 January 2010

Case Number: W 0036/08 - 3.3.04

Application Number: PCT/IB 2007/002363

Publication Number: WO 2008/010083

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Diagnostic method

Applicant:
Progenika Biopharma S.A.

Headword:
Diagnostic method/PROGENIKA

Relevant legal provisions:
PCT Art. 16, 17(3)(a), 34(3)(a)
PCT R. 13.1, 13.2, 13.3, 40.1, 40.3(e), 68.2

Relevant legal provisions (EPC 1973):
-

Keyword:
"Lack of unity - no"

Decisions cited:
G 0001/89, W 0006/90, W 0016/08

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0036/08 - 3.3.04

International Application No. PCT/IB 2007/002363

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 20 January 2010

Appellant: Progenika Biopharma S.A.
Ibaizabal Bidea-Edificio 801A 2a Planta
Parque Tecnológico de Zamudio
E-48160 Derio (ES)

Representative: Bufton, Karen A. J.
Mewburn Ellis LLP
33 Gutter Lane
London
EC2V 8AS (GB)

Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 20 February 2008.**

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
T. Bokor

Summary of Facts and Submissions

I. International patent application no. PCT/IB2007/002363 published as WO 2008/010083 and having the title "Diagnostic method" was filed on 12 July 2007 with 108 claims.

II. Independent claims 1 and 2 read as follows:

"1. A method of prognosing an osteoporosis phenotype in a subject, which comprises:
(I) obtaining outcomes for one or more single nucleotide polymorphism variables and one or more clinical variables for the subject; and
(II) using the outcomes obtained in (I) to prognose the phenotype; wherein:
(a) the osteoporosis phenotype is a presence of one or more non-traumatic fractures in the wrist, hip or spine (WSHfractures) and the variables for which outcomes are obtained in step (I) comprise
the general BSTEP model variables in Figure 9; and/or
(b) the osteoporosis phenotype is a presence of one or more non-traumatic fractures in the wrist, hip or spine (WSHfractures) and the variables for which outcomes are obtained in step (I) comprise the general FSTEP model variables in Figure 9; and/or
(c) the osteoporosis phenotype is a presence of one or more non-traumatic fractures in the wrist, hip or spine (WSHfractures) and the variables for which outcomes are obtained in step (I) comprise the male BSTEP model variables in Figure 9; and/or
(d) the osteoporosis phenotype is a presence of one or more non-traumatic fractures in the wrist, hip or spine (WSHfractures) and the variables for which outcomes are

obtained in step (I) comprise the male FSTEP model variables in Figure 9; and/or
(e) the osteoporosis phenotype is a presence of one or more non-traumatic fractures in the wrist, hip or spine (WSHfractures) and the variables for which outcomes are obtained in step (I) comprise the female BSTEP model variables in Figure 9; and/or
(f) the osteoporosis phenotype is a presence of one or more non-traumatic fractures in the wrist, hip or spine (WSHfractures) and the variables for which outcomes are obtained in step (I) comprise the female FSTEP model variables in Figure 9; and/or
(g) the osteoporosis phenotype is presence of one or more non-traumatic vertebral factures and the variables for which outcomes are obtained in step (I) comprise the male vertebral factures variables or the female vertebral factures variables in Table 5;
and wherein
(i) an outcome for an SNP variable is the identity of the nucleotide in the genomic DNA of the subject at the position of the single nucleotide polymorphism;
(ii) an outcome for the clinical variable AGE is age of the subject in years;
(iii) an outcome for the clinical variable MENOPAUSE AGE is the age in years of the onset of menopause in a female subject;
(iv) an outcome for the clinical variable MENARCHE AGE is the age in years of the onset of menarche in a female subject;
(v) an outcome for the clinical variable BMI is the body mass index of the subject."

"2. A method of estimating an osteoporosis quantitative trait in a subject, which comprises:

(I) obtaining outcomes for one or more single nucleotide polymorphism variables and one or more clinical variables for the subject; and
(II) using the outcomes obtained in (I) to estimate the trait; wherein:
(a) the quantitative trait is lumbar spine bone mineral density (LSBMD) and the variables for which outcomes are obtained in step (I) comprise the male or female LSBMD variables in Table 5; and/or
(b) the quantitative trait is femoral neck bone mineral density (FNBMD) and the variables for which outcomes are obtained in step (I) comprise the male or female FNBMD variables in Table 5; and wherein
(i) an outcome for an SNP variable is the identity of the nucleotide in the genomic DNA of the subject at the position of the single nucleotide polymorphism;
(ii) an outcome for the clinical variable AGE is age of the subject in years;
(iii) an outcome for the clinical variable MENOPAUSE AGE is the age in years of the onset of menopause in a female subject;
(iv) an outcome for the clinical variable MENARCHE AGE is the age in years of the onset of menarche in a female subject;
(v) an outcome for the clinical variable BMI is the body mass index of the subject."

Dependent claims 5 to 9 define further embodiments of the methods in accordance with claims 1 or 2.

Claims 10 to 108 relate to methods for deriving a probability function or linear functions and computational methods for use in predicting or prognosing an osteoporosis trait in a subject, to

methods of genotyping or treating osteoporosis, and to probes, primers, kits and microarrays.

Figure 9 referred to in claims 1 and 2 list various "FSTEP" and "BSTEP" model variables, while Table 5 referred to in claim 2 list 112 single nucleotide polymorphisms (SNPs) belonging to 57 different genes.

III. On 20 February 2008, the European Patent Office (EPO), acting in its capacity as International Searching Authority (ISA) under Article 16 PCT and Article 154 EPC informed the applicant in an invitation under Article 17(3) (a) PCT and Rule 40.1) PCT that the application did not comply with the requirement of unity of invention (Rule 13.1 PCT) and invited the applicant to pay within a time limit of one month hundred and eleven (111) additional search fees.

IV. In the invitation to pay additional fees, the ISA defined the hundred and twelve (112) inventions to which the application related as follows:

INVENTION 1:

claims: 1-108 (partially)

Probes, primers, microarrays and method for prognosing, genotyping and treating osteoporosis using polymorphism rs2234693 of estrogen receptor (ESR1) in Fig. 9.

INVENTIONS 2—112:

claims: 1-108 (partially)

Probes, primers, microarrays and method for prognosing, genotyping and treating osteoporosis using the polymorphisms listed in Fig. 9 and Table 5, for each polymorphism in an identified gene separately. Table 5 has been identified to refer to 57 different genes and 112 single nucleotide polymorphisms (SNPs), see page 15, lines 21-31.

V. The ISA referred in the invitation to the following documents:

D1 WO-A-00/15836;

D2 WO-A-97/27321;

D3 US-A-2006/0057612;

D4 WO-A-03/066903;

D5 Kobayashi S. et al., J. Bone and Mineral Research, Vol. 11, No. 3, pages 306-311 (1996);

D6 Gennari L. et al., Am. J. Epidemiology, Vol. 161, No. 4, pages 307-320 (2005);

D7 WO-A-2004/097044;

D8 WO-A-2004/046381;

D9 Ioannidis J.P.A. et al., JAMA, Vol. 292, No. 17, pages 2105-2114 (2004).

VI. The ISA defined the common concept of the application as the prognosis of osteoporosis by evaluating one or

more of the 112 SNP's single nucleotide polymorphisms (SNP's) belonging to 57 different genes listed in Fig. 9 and Table 5 and page 15, lines 21 onwards.

However, the ISA argued that nucleotide polymorphisms of various genes were already known from the prior art to be suitable markers for evaluating a susceptibility for osteoporosis. For instance, document D1 described a method for determining the susceptibility to osteoporosis by detecting polymorphisms in the estrogen receptor and the vitamin D receptor gene. Document D2 also disclosed the use of the estrogen receptor polymorphisms for evaluating an osteoporosis predisposition. Document D3 disclosed a method for evaluating the susceptibility to osteoporosis by haplotyping the BMP2 gene. Document D4 related to genetic markers for predicting osteoporosis by evaluating SNPs in the TCIGR1 gene. Document D5 described PvuII and XbaI restriction markers for evaluating bone mineral density. Document D6 discussed the relation between ER polymorphisms and osteoporosis. Document D7 described polymorphisms in the INHBA gene and their relation to bone damage (osteoporosis). Document D8 referred to polymorphisms in the CLCN7 gene as suitable marker for osteoporosis. Finally, document D9 already discussed the rs2234693 polymorphism as marker for evaluating osteoporosis.

In addition, the ISA noted that no further structural and/or functional features of the claimed subject—matter of claims 1—108 in comparison to the cited prior art (documents D1 to D9) could be identified to link the claimed subject—matter to form a single general inventive concept. Therefore the claimed subject—matter

had to be split up in several inventions as identified above. Since claim 1 a) referred to the BSTEP model of Fig. 9 which mentioned the rs2234693 polymorphism first, this SNP was identified the ISA as the first invention.

VII. The communication dated 20 February 2008 also contained the results of the partial international search which was established for the invention first mentioned in the claims, i.e. "invention 1" relating to probes, primers, microarrays and method for prognosing, genotyping and treating osteoporosis using polymorphism rs2234693 of estrogen receptor (ESR1) in Fig. 9.

VIII. With a letter dated 20 March 2008, the applicant paid one additional search fee under protest, while requesting an additional search for the invention relating to the polymorphism rs1801197 in the calcitonin receptor gene (SNP 39 in Table 5 and Table 1B of the application).

The applicant argued that the common inventive concept linking the alternative models in claims 1 and 2 was the provision of a multivariate model, based on a combination of SNP(s) **and** clinical variable(s), for the prediction of an osteoporosis-associated phenotype or trait.

There was no disclosure in any of documents D1 to D9 of a model for predicting a fractures phenotype, based on a combination of SNP(s) **and** clinical variable(s) as in claim 1, or a model for predicting bone mineral density based on a combination of SNP(s) and clinical variable(s) as in claim 2.

Therefore, there was unity between the alternative tests in the claims, all parts of which should have been searched.

The applicants requested the reimbursement of the additional search fee and that the ISA withdraws the objection for lack of unity and searches the invention as claimed with respect of all parts of the claims.

The applicant further submitted that, at the very least, the subject-matter of claim 1, part (a) was unified and should have been searched in its entirety on payment of the first search fee.

IX. On 3 June 2008, the ISA invited the applicant to pay a protest fee and informed the applicant that a prior review of the justification for the invitation to pay additional fees had confirmed that the invitation to pay such fees was justified.

In the annex to the invitation to pay the protest fee the review panel noted that the use of clinical variables (e.g. age) for evaluating osteoporosis could not be acknowledged as an additional structural/ functional feature in comparison to the cited prior art for supporting the requirements for the provision of a general single inventive concept, because the prior art (see e.g. document D1 on page 37) already considered the clinical variable "age" as a factor for evaluating the prognosis to osteoporosis.

X. With letter of 2 July 2008, the applicant authorised the ISA to charge its deposit account for the payment

of the protest fee and argued in response to the notification of the review panel.

Reasons for the Decision

Competence and admissibility

1. Given that the application was filed on 12 July 2007, the protest is subject to the provisions of the PCT as in force from 1 April 2007. The boards of appeal are responsible for deciding on protests relating to PCT applications pending at the time of entry of the EPC 2000. Details of the procedure are guided by the Decision of the President of the EPO dated 24 June 2007, Article 3 (OJ EPO 2007, Special Edition No. 3, 140), see also W 16/08, points 1.1 to 1.5 of the reasons.

2. The invitation under Article 17(3) (a) PCT to pay additional fees is reasoned in accordance with Rule 40.1 PCT.

3. The protest against the invitation by the ISA to pay additional fees was filed in time, is reasoned and is hence admissible.

Substantive matters

4. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims lack unity of invention, it is empowered, under

Article 17(3)(a) PCT, to invite the applicant to pay additional fees.

5. According to Rule 13.2 PCT, where a group of inventions is claimed in one and the same application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, whereby the expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

6. According to Rule 13.3 PCT the determination of whether a group of inventions is so linked as to form a single inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

7. Lack of unity may be directly evident a priori, i.e. before the examination of the merits of the claims in comparison with the state of the art revealed by the search (see for example, decision W 6/90, OJ EPO 1991, 436). Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal (OJ EPO 1991, 155), the ISA may also raise an objection a posteriori, i.e. after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT International Search Guidelines (Chapter 10, pages 75 to 100) which are the basis for a uniform practice of all international search authorities. In its decision, the Enlarged Board of Appeal indicated that such consideration represents

only a provisional opinion on novelty and inventive step which is in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1. of the Reasons for the decision). In point 8.2 of the Reasons, the Enlarged Board mentioned that such invitation to pay additional fees should always be made "with a view to giving the applicant fair treatment" and should only be made in clear cases.

8. The question to be decided by the board here is whether the subject-matter of those inventions for which search fees have been paid by the applicant, namely the invention identified by the ISA as "invention 1" relating to probes, primers, microarrays and method for prognosing, genotyping and treating osteoporosis using polymorphism rs2234693 of estrogen receptor (ESR1) in Fig. 9 and the invention (hereafter: "invention 2") identified by the ISA and elected by the applicant relating to probes, primers, microarrays and method for prognosing, genotyping and treating osteoporosis using polymorphism rs1801197 in the calcitonin receptor gene SNP 39 in Table 5 and Table 1B of the application (see paragraphs VII and VIII above), are so linked as to form a single inventive concept or not.

9. In the present case, the ISA's invitation to pay additional fees is based on the opinion that documents D1 to D9 disclose all the features of the subject matter of claims 1 and 2 (see paragraph VI above), which opinion has been contested by the applicant. Therefore, the board has to examine the relevance of the prior art identified.

10. Document D1 focuses on markers in the estrogen receptor (ER) and the vitamin D receptor (VDR) genes, and their association with bone mineral density (BMD) and bone density (BD).

Document D2 is concerned with methods for determining predisposition to low or high BMD based on determining polymorphism in the ER gene.

Document D3 identifies a number of haplotypes of the BMP2 (human bone morphogenetic protein 2) genes associated with hip, vertebral or other osteoporosis-related low impact fractures.

Document D4 is concerned with determining BMD based on allelic variations in the TCIRG1 gene.

Document D5 focuses on the PvuII and XbaI restriction length fragment polymorphisms (RFLPs) of the estrogen receptor (ER) gene and their relationship to BMD. RFLPs are different from the SNPs referred to in the present claims.

Document D6 relates to polymorphisms in the estrogen receptor genes ERα and ERβ, and their association with osteoporosis.

Document D7 refers to a specific polymorphism at position 39 in the INHBA gene (Inhibin beta-A) and the use of this polymorphism in the diagnosis of susceptibility to fractures and bone damage.

Document D8 is concerned with a number of allelic variations in the CLCN7 gene (chloride channel 7)

identified by the authors of this document as associated with BMD.

Document D9 investigates on whether 3 common ESR1 polymorphisms, namely XbaI (rs9340799), PvuII (rs2234693) and (TA) (rs3138774) are associated with BMD and fractures.

11. However, none of documents D1 to D9 discloses any model for predicting a fractures phenotype, based on a combination of SNP(s) and clinical variable(s) as in claim 1, or any model for predicting bone mineral density based on a combination of SNP(s) and clinical variable(s) as in claim 2.

As a matter of fact, the reasoning in the invitation to pay further fees does not consider at all the above-mentioned aspect ("combination of SNP(s) and clinical variable(s)") and the communication from the Review Panel merely states that "the prior art (see e.g. document D1 on page 37) already considered the clinical variable "age" as a factor for evaluating the prognosis of osteoporosis" (see paragraph XI above), without taking into account the fact that claims 1 and 2 require a combination of SNP(s) **and** clinical variable(s).

As stressed by the applicant in its letter dated 20 March 2008 and as transpires from the application (see claims 1 and 2 and e.g., page 6, lines 17-18), this aspect is, however, a key feature of the claimed invention.

12. Given the novelty of claims 1 and 2 vis-à-vis documents D1 to D9, in order to now decide whether or not there is still a common technical link between invention 1 and 2 (see point 8 above) justifying the finding of unity of the invention, an examination of the inventive step would be necessary because only when this is acknowledged, it is possible to accept a linking inventive concept. However, this cannot be considered a "clear case" as required by decision G 1/89 (see point 7 supra). In order that the Applicant be given "fair treatment" (see point 7 supra), the board does not carry out this examination.

13. In conclusion, the board cannot follow the ISA's reasoning, according to which the searched subject-matter lacks unity of invention. Hence, the invitation provided for in Article 34(3)(a) and Rule 68.2 PCT to pay an additional search fee was not properly founded.

14. The Board therefore finds the applicant's protest entirely justified so that the additional fee and the protest fee must be refunded in accordance with Rule 40.3(e) PCT.

Order

For these reasons it is decided that:

The additional search fee and the protest fee are to be reimbursed.

The Registrar | The Chair

P. Cremona | U. Kinkeldey