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Datasheet for the decision of 7 December 2022

Case Number: T 1992/21 - 3.3.04

Application Number: 13175987.0

Publication Number: 2676967

IPC: C07K16/28, A61K39/395, G01N33/53, G01N33/68, A61K39/00, A61K38/21, A61K38/03, A61K45/06, A61K49/00

Language of the proceedings: EN

Title of invention:
Methods of treating inflammatory and autoimmune diseases with natalizumab

Patent Proprietor:
Biogen MA Inc.

Opponent:
Polpharma Biologics S.A.

Headword:
Natalizumab and PML/BIOGEN

Relevant legal provisions:
RPBA 2020 Art. 12(4), 12(6)
EPC Art. 56

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Keyword:
Amendment to case - reasons for submitting amendment in appeal proceedings (no)
Inventive step - (no)

This datasheet is not part of the Decisior
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Case Number: T 1992/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 December 2022

Appellant: (Patent Proprietor)	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 (US)
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Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 October 2021 revoking European patent No. 2676967 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. An appeal was lodged by the patent proprietor (appellant) against the opposition division's decision revoking European patent No. 2 676 967 (hereinafter "the patent") entitled "*Methods of treating inflammatory and autoimmune diseases with natalizumab*".

Claim 1 of the patent as granted reads:

"1. Natalizumab for use in treating an inflammatory or autoimmune disease in a patient, wherein plasma or serum from a blood sample of the patient has been tested for the presence of IgG antibodies to JC virus, and wherein the treatment is initiated in the event that the sample is negative for IgG antibodies to JCV."

II. The opposition proceedings were based on the grounds under Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and Article 100(b) and 100(c) EPC.

III. In its decision the opposition division, *inter alia*, held that the subject-matter of claim 1 of the main request (patent as granted) and of auxiliary request 5 extended beyond the content of both the application as filed and the earlier application. The subject-matter of claim 1 of auxiliary requests 1 to 4 and 6 to 19 lacked an inventive step over the disclosure of document D7.

IV. With the statement of grounds of appeal, the appellant re-filed auxiliary requests 1 to 19 which had been dealt with in the decision under appeal, and filed new auxiliary requests 20 to 25 as well as document D46.

Claim 1 of auxiliary request 1 reads:

"1. Natalizumab for use in treating an inflammatory or autoimmune disease in a patient, wherein plasma or serum from a blood sample of the patient has been tested for the presence of IgG antibodies to JC virus, wherein the treatment is initiated in the event that the sample is negative for IgG antibodies to JCV; wherein the patient is monitored for indicators of progressive multifocal leukoencephalopathy (PML) and if indicators of PML are present, administration of natalizumab is discontinued."

Claim 1 of auxiliary requests 2 to 4 further defines the indicators of PML.

Claim 1 of auxiliary requests 5 to 9 further specifies that the disease is multiple sclerosis (MS).

Claim 1 of auxiliary requests 10 to 13 further specifies "wherein the monitoring comprises serially removing samples of the patient's blood, measuring the amount of IgG antibodies to JCV in the samples, and comparing the amount of the antibodies in the samples".

Claim 1 of auxiliary requests 14 to 17 further defines the indicators of PML.

Claim 1 of auxiliary requests 18 and 19 combines the features of claim 1 of auxiliary requests 12 and 15, and 12 and 17, respectively.

Claim 1 of auxiliary requests 20 to 25 combines claim 1 of auxiliary requests 7 and 14, 8 and 15, 8 and 16, 9 and 17, 13 and 18, and 13 and 19, respectively.

V. The opponent (respondent) replied to the appeal.

VI. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

VII. In this communication the board *inter alia* opined that claim 1 of the main request extended beyond the content of the application as filed and that the subject-matter of claim 1 of auxiliary requests 1 to 19 and 20 to 25 (if admitted) lacked an inventive step over the disclosure of document D7 in combination with the disclosure of document D28.

VIII. In a letter dated 4 November 2022, the appellant replied to the board's preliminary opinion and the respondent's reply to the appeal.

IX. In a letter dated 23 November 2022, the respondent replied to the appellant's letter and filed document D47.

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

XI. The following documents are cited in the present decision:

D7 J. R. Berger and I. J. Koralnik, "*Progressive Multifocal Leukoencephalopathy and Natalizumab – Unforeseen Consequences*", New England Journal of Medicine 2005, 353:414-416

D8B W. A. Knowles, "*Discovery and Epidemiology of the Human Polyomaviruses BK Virus (BKV) and JC Virus (JCV)*", Chapter 2 in "*Polyomaviruses and human diseases*" edited by Nasimul Ahsan, Advances in Experimental Medicine and Biology, Volume 577, published on 2 February 2006, 19-45

D8D J. Hou, P. Seth and E. O. Major, "*JC Virus Can Infect Human Immune and Nervous System Progenitor Cells: Implications for Pathogenesis*", Chapter 19 in "*Polyomaviruses and human diseases*" edited by Nasimul Ahsan, Advances in Experimental Medicine and Biology, Volume 577, published on 2 February 2006, 266-273

D8E N. Ahsan and K. V. Shah, "*Polyomaviruses and Human Diseases*", Chapter 1 in "*Polyomaviruses and human diseases*" edited by Nasimul Ahsan, Advances in Experimental Medicine and Biology, Volume 577, published on 2 February 2006, 1-18

D15 L. Gorelik et al., "*Anti-JC Virus Antibodies: Implications for PML Risk Stratification*", Annals of Neurology 2010, 68:295-303

D19 Declaration of Professor Dr Berger

D21 S. M. Gillespie et al., "*Progressive Multifocal Leukoencephalopathy in Persons Infected with Human Immunodeficiency Virus, San Francisco, 1981-1989*", Annals of Neurology 1991, 30(4):597-604

D22 W. A. Knowles et al., "*Prevalence of Long-Term BK and JC Excretion in HIV-Infected Adults and Lack of Correlation With Serological Markers*", Journal of Medical Virology 1999, 59:474-479

D27 Annex with data generated at Biogen (2012)

D28 T. Weber et al., "*Analysis of the Systemic and Intrathecal Humoral Immune Response in Progressive Multifocal Leukoencephalopathy*", Journal of Infectious Diseases 1997, 176:250-254

D38 Yael Waknine. Tysabri Suspended From U.S. Market, Medscape Medical News, 28 February 2005

D39 Supplementary Appendix of Yousry TA et al., 2006. NEJM. 354(9):924 (D20); Biogen's notice to health practitioners

D46 A. Chaudhuri, "*Lessons for clinical trials from natalizumab in multiple sclerosis*", British Medical Journal, 6 February 2006, 332:416-419

XII. The appellant's arguments, as far as relevant to the decision, may be summarised as follows.

Admission of document D46

Document D46 was filed at the earliest possible opportunity, namely with the statement of grounds of appeal. It was a direct response to the opposition division's finding that the technical effect of a safer treatment with natalizumab was not plausible. This only became apparent during the oral proceedings and from the opposition division's written decision.

Document D46 was *prima facie* relevant as it questioned whether JCV-naive MS patients could be treated with natalizumab. Document D46 was common general knowledge as it represented an expert opinion on the state of the art in the field and cited several documents relevant in the appeal in hand (e.g. D4, D5, D6 and D7).

Main request and auxiliary request 1 - claim 1
Inventive step (Article 100(a) EPC and Article 56 EPC)

The skilled person would have been reluctant to try natalizumab in any new patient group without having the benefit of the safety assessment results that were disclosed in the patent. Thus, selecting a patient group for initiating treatment with natalizumab would not have been trivial or routine.

Considering document D7 as the closest prior art, several differences were apparent:
1) type of test (JCV DNA vs JCV antibody, specifically IgG)
2) timing of the test (during natalizumab treatment vs before natalizumab treatment)

3) initiating treatment in the JCV antibody-negative patient group (instead of all natalizumab-treated patients)
4) monitoring the JCV antibody-negative patient group (only for auxiliary request 1)

The standard approach for JCV detection at the priority date entailed detecting JCV DNA in a patient sample. Prior art relating to assessing PML in HIV/AIDS patients, in whom PML was more frequently found than in autoimmune disease patients taking natalizumab, also disclosed detecting JCV DNA. There was thus no reason or incentive to depart from this accepted method.

Document D7 taught retrospective and prospective analyses of blood in natalizumab-treated patients (i.e. testing the blood of patients already on natalizumab; see page 416, left-hand column, second and third full paragraphs), but not testing patients before natalizumab therapy had been initiated.

The skilled person reading document D7 would thus not have considered JCV antibody status as a possible marker for PML in order to make a treatment decision.

Moreover, the other prior art lacked any suggestion to use JCV antibodies for predicting or diagnosing PML (documents D21, D22, the textbook D8E and document D28).

There was no preference for using blood as a source for detecting JCV for the purpose of diagnosing and/or monitoring PML. Urine, which was at least as convenient as blood for sampling patients, was a commonly used alternative. Cerebrospinal fluid (CSF) samples were the

choice for diagnosing PML and thus a proven way of linking JCV viral load to PML.

At the priority date, natalizumab treatment had been voluntarily suspended due to the PML risk. The risk of PML for JCV-naive patients was not known, while the prior art expressed doubts that natalizumab could be safely used to treat MS at all (see e.g. D7). The skilled person would therefore not have proceeded in any such patient group without a clear instruction or pointer in the prior art to do so.

These safety concerns were removed with the patent's disclosure of the results of the safety trials in over 3 000 patients. The patent showed that blocking the "rescuers at the gate" (see document D7, page 416, last paragraph) was not associated with PML risk, as disclosed in the prior art. The skilled person would not have viewed natalizumab as a safe treatment option for patients until they had become aware of the teachings of the patent.

The patent taught, for the first time, that testing for JCV DNA in plasma or serum was not predictive for PML in patients receiving natalizumab. The patent disclosed for the first time that testing for the presence of IgG antibodies in serum or plasma of the sample "*improve[d] the safety of the treatment*" (paragraph [0021]). This was confirmed by post-published data (see documents D15 and D27).

The declaration by Dr Berger (an author of document D7) provided as document D19 showed that D7 did not propose detecting JCV antibodies to predict the risk of PML (see item 20 of D19). The reference to document D28 in document D7 was thus only with regard to the

seroprevalence of JCV and not to the detection of JCV IgG for making a treatment decision.

Auxiliary requests 2 to 25 - claim 1
Inventive step (Article 56 EPC)

Like auxiliary request 1, auxiliary requests 2 to 4 and 6 to 25 specified that the patient was monitored for indicators of PML and that administration of natalizumab was discontinued if indicators of PML were detected. Auxiliary requests 5 to 9, 11, 13 and 20 to 25 specified that the disease was MS, which further distinguished the subject-matter over the prior art.

Auxiliary requests 10 to 13, 18, 19, 24 and 25 distinguished the claimed subject-matter even further since there was nothing in the prior art that taught or suggested assessing a patient's risk of developing PML by "s*erially removing samples of the patient's blood, measuring the amount of IgG antibodies to JCV in the samples, and comparing the amount of the antibodies in the samples*". The application referred to seroconversion in paragraph [0036], defining it as "*the change of a serologic test from negative to positive, indicating the development of antibodies*". None of the prior-art documents anticipated the possibility of seroconversion of a patient's JCV status or disclosed that seroconversion should be monitored in order to minimise the risk of PML.

Auxiliary requests 12, 13, 18, 19, 24 and 25 combined seroconversion monitoring with testing for clinical and/or radiological symptoms of PML. This combination of measures, which had the technical effect of improving the safety of natalizumab treatment even further, was not suggested by the prior art.

XIII. The respondent's arguments, as far as relevant to the decision, may be summarised as follows.

Admission of document D46

In its statement of grounds of appeal the appellant only indicated that the document was "*submitted in direct response to the reasoning denying inventive step of the OD*", but did not explain which aspects were new in the decision under appeal. And in its letter of 4 November 2021, it did not provide any cogent reasons why document D46 could not have been filed earlier.

Document D46 did not go beyond the teaching of document D7. This was also apparent from the statement of grounds of appeal, in which the appellant always cited both documents together and did not highlight specific aspects of the disclosure of document D46.

Document D46 could not be considered common general knowledge as it was a letter in the section "Analysis and Comment" of a scientific journal, so it could only be considered a personal opinion of an individual researcher.

As early as in its preliminary opinion (dated 7 December 2020), the opposition division had indicated that it was obvious that patients who had never contracted JCV were safer to treat with natalizumab (see sheet 11).

Lastly, the focus of document D46 was whether MS patients should be treated with anti-inflammatory immunotherapy at all, so the document was irrelevant.

Main request and auxiliary request 1 - claim 1
Inventive step (Article 100(a) EPC and Article 56 EPC)

The link between JCV latency (as detectable through JCV seropositivity, i.e. the presence of anti-JCV IgG antibodies in serum), immunosuppression through treatment with immunosuppressive drugs, reactivation of JCV and development of PML formed part of the common general knowledge. The skilled person knew that testing for IgG antibodies against JCV was routinely used to assess seropositivity to JCV in a patient.

The skilled person thus knew that people infected with JCV had a predisposition to developing PML while people who were not infected with JCV could not develop PML. Thus, it was obvious and trivial to treat only people without that risk.

The opposed patent did not provide any supporting data which would go beyond said known fact.

The subject-matter of claim 1 differed from the disclosure of document D7 by explicitly referring to the treatment of seronegative patients, which had the technical effect of safer treatment. The monitoring of PML during treatment was also directly and unambiguously disclosed at least in document D7.

The objective technical problem might therefore be considered that of providing a safer natalizumab treatment for inflammatory and autoimmune diseases, in particular MS.

The solution was obvious when starting from document D7, which stated in the first paragraph that natalizumab treatment can cause PML by reactivating a

clinically latent JCV infection. This clearly taught that only patients who had a JCV infection were at risk of developing PML. In turn, patients who were not infected were not at risk of developing PML. It was thus obvious and trivial that a seronegative patient group would not be at risk of developing PML; in other words, treating seronegative patients was associated with fewer risks than treating seropositive patients.

Document D7 also taught the skilled person that testing JCV serostatus was a predictive and preventive measure for safer natalizumab treatment as patients who had tested seronegative beforehand were not at risk of developing PML and might therefore be treated without risk (see document D7, page 416, first full paragraph).

This was supported by Dr Berger (one of the authors of document D7), who stated that he had indeed been contemplating testing for serum JCV antibodies when writing document D7, i.e. before the priority date (see item 11 of document D19). Hence, testing for serum JCV antibodies before treatment was an obvious measure, as taught by D7 and confirmed by D19.

Dr Berger also provided clear reasoning why he decided not to pursue said obvious measure any further, namely that only a minority of patients (14 to 50%) could have been treated when choosing this precautionary route.

The patent did not provide any data showing that IgG status was a valid marker of PML risk. Paragraphs [0021] and [0024] taught the exact opposite with regard to the patient group to be treated: paragraph [0021] taught that patients testing negative were to be treated whereas paragraph [0024] taught that patients testing positive were to be treated. This mutually

exclusive teaching was further underlined by claims 20 and 40 of the parent application as filed.

Even if the monitoring of PML during treatment was considered to represent a difference, it was obvious in view of document D7, which suggested monitoring for clinical symptoms of PML (namely the presence of JCV DNA in the patient's serum) and interrupting/ discontinuing treatment with natalizumab if indicators of PML were found (see page 416, left-hand column, penultimate paragraph).

Auxiliary requests 2 to 25 - claim 1
Inventive step (Article 56 EPC)

All measures for detecting indicators of PML were well known to the skilled person. Hence, an inventive step could not be based on the differential diagnosis of MS and PML either. Moreover, the monitoring of clinical/ radiological signs of PML was mandatory at the time (see also documents D38 and D39). Serially removing and testing samples could not be equated with seroconversion because it encompassed any increase or decrease in antibodies as well as a more or less static level and the complete lack of antibodies in two samples. As the comparison was completely undefined and arbitrary, there was no causal link to the potential discontinuing step either. Hence, the treatment with natalizumab was continued regardless of the outcome of the comparison, and no technical effect could be attributed to this feature.

Even if the feature of serially removing and testing samples were interpreted in the sense of detecting seroconversion, it was obvious. As exposure to JCV could occur at any point in life (see document D8B,

abstract on page 19) and PML often had fatal consequences, it was mandatory for the skilled person to monitor patients for seroconversion when treating them with natalizumab, which was administered over many years.

XIV. The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request which is the patent as granted, or, on the basis of the sets of claims of auxiliary requests 1 to 19, which are the sets of claims underlying the decision under appeal, or further alternatively on the basis of the sets of claims of auxiliary requests 20 to 25, submitted with the grounds of appeal. The appellant requested further that document D46 be admitted into the proceedings, that document D40 not be taken into account, and finally, in case that document D40 were to be taken into account, that also document D43 be taken into account.

XV. The respondent (opponent) requested that the appeal be dismissed and that auxiliary requests 20 to 25 and documents D43 and D46 not be admitted into the proceedings.

Reasons for the Decision

Admission of document D46 (Article 12(4) and (6) RPBA)

1. Document D46 was filed with the statement of grounds of appeal and represents an amendment to the appellant's appeal case (Article 12(4) RPBA). In the statement of grounds the appellant explained that "*D46 is submitted in direct response to the reasoning denying inventive*

step of the OD in the Decision". This statement, however, neither identifies the alleged new reasoning given by the opposition division in the decision nor explains why document D46 was required in order to respond to the decision.

2. The appellant provided further reasoning in a letter dated 4 November 2022 ("*D46 is a direct reaction to the Decision of the OD denying inventive step, since it highlights the strong doubts about using natalizumab at the priority date*") and during oral proceedings. This further justification, however, represents an amendment to the appeal case made after notification of a summons to oral proceedings. Under Rule 13(2) RPBA any such amendment is, in principle, not to be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned. The appellant has not asserted any exceptional circumstances.

3. For these reasons alone the board did not admit document D46 into the proceedings.

4. Moreover, as pointed out by the respondent, the opposition division in its preliminary opinion dated 7 December 2020 had already indicated that "*the choice of JCV-negative patients as a more promising subgroup appears obvious*". The opposition division's position on inventive step was thus already apparent before the oral proceedings in opposition. Lastly, in its statement of grounds of appeal the appellant always cited document D46 together with document D7 and did not point to any additional information going beyond the teaching of document D7 (see pages 14, 17, 19, 35 and 36 of the statement of grounds of appeal). Therefore, in view also of the need for procedural

economy, the board saw no reason to admit document D46 into the proceedings.

Auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)
Closest prior art and differences

5. The features of claim 1 can be separated as follows:

A Natalizumab for use in treating an inflammatory or autoimmune disease in a patient,
B wherein plasma or serum from a blood sample of the patient has been tested
C for the presence of IgG antibodies to JC virus,
D and wherein the treatment is initiated in the event that the sample is negative for IgG antibodies to JCV,
E wherein the patient is monitored for indicators of progressive multifocal leukoencephalopathy (PML),
F and if indicators of PML are present, administration of natalizumab is discontinued.

6. The parties agree that document D7 is the closest prior art because it aims at a safer treatment of inflammatory or autoimmune diseases with natalizumab.

7. Document D7 reviews the reports of three cases of PML which occurred during clinical trials of natalizumab for treating MS or Crohn's disease. It points out that PML "*is caused by reactivation of a clinically latent JC polyomavirus infection*" (see page 414, left-hand column) and states that since "*the present reports did not provide data on the serological status of JC virus for the patients, we can only assume that the patients had been infected in childhood*" (see page 414, right-hand column, first full paragraph). The authors discuss

the possible role played by natalizumab in the development of PML, reasoning that it "*appears likely that natalizumab, by preventing normal trafficking of lymphocytes, led to unbridled JC virus replication*" (see page 414, right-hand column, last paragraph).

8. The parties agree that feature A is disclosed in document D7 (see e.g. page 414, left-hand column, first paragraph: "*natalizumab for the treatment of multiple sclerosis or Crohn's disease*"). The parties also agree that feature D represents a difference because document D7 does not disclose initiating the treatment with natalizumab in the event that the sample is negative for IgG antibodies to JCV.

9. Feature B equally represents a difference because document D7 only reports that "*the rate of seropositivity for this virus* [i.e. JCV] *is from 50 to 86 percent in healthy adults*". This is a statistical estimate for a population obtained by testing a sample group, but it does not disclose testing an individual patient before treatment as required in claim 1 ("has been tested"). By referring to "*seropositivity for this virus*" document D7 discloses that a part of the population carries antibodies against JCV in their blood serum, without specifying the isotype of those antibodies (i.e. IgG). This means that D7 does not disclose feature C either ("IgG antibodies to JCV").

10. Document D7 discloses monitoring patients irrespective of their serological status, for example on page 414, left-hand column, third full paragraph: "*imaging findings of a multifocal process ... should always raise the suspicion of PML*" and "*polymerase chain reaction (PCR) for JC virus in the cerebrospinal fluid*

establishes the diagnosis when coupled with the appropriate clinical and radiologic features". Furthermore, document D7 reports discontinuing the treatment following a PML diagnosis (see page 414, right-hand column, first full paragraph: "*treatment with natalizumab was eventually discontinued in the three patients*") and that "*the prospective measurement of the JC viral load in plasma and the preemptive reduction of doses or interruption of treatment if JC virus DNA appears in the blood might actually prevent the development of PML in this setting*" (see page 416, left-hand column, third full paragraph). Document D7 thus discloses monitoring patients treated with natalizumab and discontinuing the treatment when indicators of PML are present. The board does not agree with the appellant that features E and F represented a further difference because monitoring was performed on a new patient group. As the patient group already constitutes a difference (feature D) between the claimed medical use and the disclosure of document D7, it cannot represent a further difference in features E and F.

11. In summary, the claimed subject-matter differs from the disclosure in document D7 in that plasma or serum from a blood sample of the patient has been tested (feature B) for the presence of IgG antibodies to JC virus (feature C) and the treatment is initiated in the event that the sample is negative for IgG antibodies to JCV (feature D).

Effect and objective technical problem

12. The parties agree that the effect of these differences is a safer treatment (see points 41, 43, 87, 123 and

125 of the statement of grounds of appeal and points 121, 122 and 261 of the reply to the appeal).

13. The parties also agree that the objective technical problem can be formulated as providing a safer treatment for inflammatory or autoimmune diseases with natalizumab (see e.g. points 60 and 123 of the statement of grounds of appeal and point 261 of the reply to the appeal).

14. In acknowledging the above objective technical problem, the board rejects the opposition division's conclusion that "*it is not shown that seronegativity for JCV IgG is a valid marker, nor is it made plausible. On the contrary, if as reported in [68] even JCV DNA is a poor predictor of risk, then a fortiori there is no reasonable expectation that any other marker can work effectively to allow the assessment of risk*". In coming to this conclusion the opposition division apparently misunderstood the different biological relevance of JCV DNA and antibodies against JCV. While the former indicates active virus in the blood, i.e. acute infection, the latter signals that an infection with JCV has occurred at an earlier point in life, resulting in antibodies in the blood while the virus itself remains hidden in other body compartments and is undetectable in blood, i.e. latent infection (see document D8D, paragraph bridging pages 266 and 267 and Figure 1). As the link between latent JCV infection and PML was common general knowledge at the priority date of the patent (see D8D, page 266, second paragraph) it was plausible for the skilled person that selecting patients who were seronegative for JCV would greatly reduce the risk of PML. This is further supported by evidence in later-published documents D15 and D17.

Obviousness

15. The authors of document D7 asked the following question: "*Would it be possible to predict and prevent the occurrence of PML in patients receiving alpha-4 integrin blockers?*" (see page 416, left-hand column, first full paragraph). This is immediately followed by the consideration that "[o]*nly persons infected with JC virus are at risk for PML, but the rate of seropositivity for this virus is from 50 to 86 percent in healthy adults*", which reflects the common general knowledge (see also document D8B, Table 4, showing JCV seroprevalence in various populations). This fact, however, implies that anyone not infected with JCV is not at risk of developing PML. When aiming to solve the objective technical problem of providing a safer treatment (see point 13. above) the skilled person would have recognised that the safest way to treat patients with natalizumab was to treat only those who were not at risk of developing PML, i.e. anyone not infected with JCV. By referring in this context to "*the rate of seropositivity*", document D7 also discloses how latent infection with JCV can be detected, namely by determining antibodies in blood serum. The "*but*" preceding the statement that more than half of the healthy adult population (50 to 86%) is seropositive would have been understood by the skilled person to mean that the authors were cautioning that JCV seroprevalence as a selection criterion would exclude a major part of the population from treatment with natalizumab. This is confirmed by a later declaration by one of the authors of document D7: "*I was not optimistic that testing serum JCV antibodies would be helpful, since if used, it meant that most patients could not be treated with natalizumab*" (see document D19, point 11). The skilled person, however, would have

considered this reticence irrelevant when trying to solve the objective technical problem of providing a safer treatment, which did not imply a treatment applicable to most patients.

16. As it was common general knowledge that JCV infection and thus seropositivity often occur early in life (see document D8D, page 266, penultimate and last paragraph, and Figure 1) and that the seroprevalence in the population was quite high (see document D7, supra and D8B, supra), it was also obvious for the skilled person that patients had to be tested and selected before starting natalizumab treatment. Only in that way could the treatment of persons previously infected with JCV (latent infection) be avoided.

17. By referring to "*the need for a highly sensitive, universally accepted enzyme-linked immunosorbent assay*" document D7 points to means for determining the JCV serological status in patients. In the same passage document D7 also refers to reference 16 (document D28 in this appeal). The skilled person would thus have consulted document D28, which discloses the relevant isotype of the JCV antibody in serum ("IgG") and provides means for detecting it. In particular, document D28 discloses "*ELISA analysis of paired CSF-serum samples*" using recombinant JCV VP1 protein (see document D28, page 251, left-hand column, second full paragraph) and that "*the IgG response was analyzed by a quantitative ELISA of paired cerebrospinal fluid /(CSF) and serum samples*" (see abstract). The presence of IgG antibodies (i.e. affinity-matured antibodies from memory B cells) against JCV in serum was also common general knowledge at the relevant date of the patent because in most patients the primary JCV infection is

not acute but occurred a long time ago (see document D8D, page 268, second paragraph).

18. The finding on page 252, right-hand column, of document D28 that "*seroprevalence of 100% in patients with PML further substantiates JCV as the causative agent for PML*" confirms the commonly known causative link between JCV and PML. The appellant asserted that the statement "[s]*erum antibody determination thus cannot be used to diagnose PML*" in document D28 "*provide*[d] *a disincentive*" to determine serum antibody. The board does not agree. This point is irrelevant since the objective technical problem is aimed at a safer treatment and not at PML diagnosis. In addition, document D28 would have thus led the skilled person to conclude that JCV seronegative patients had a very low risk of developing PML.

19. It would thus have been obvious to the skilled person from the disclosure of document D7 in combination with the disclosure of document D28 to select patients who were seronegative for IgG antibodies against JCV in their blood serum for treatment with natalizumab.

20. The appellant questioned whether the skilled person when reading document D7 would (and not only could) switch from testing JCV DNA as a potential predictive marker for PML in patients already treated with natalizumab to testing IgG against JCV in serum of patients before starting the treatment with natalizumab.

21. The board considers this immaterial. Document D7 does not present the two approaches as mutually exclusive, or even as representing alternatives. In analysing reports from past clinical trials, document D7

discusses a situation where natalizumab treatment had already started (see page 416, left-hand column, end of second full paragraph: "*determine whether it will be possible to fashion preventive strategies against the development of PML in patients treated with natalizumab*"). The skilled person would have recognised that, in contrast to this monitoring during treatment, the statement in document D7 that "[o]*nly persons infected with JC virus are at risk for PML*" addressed the question of which group of patients was at risk of PML in principle and which group was not, regardless of the treatment with natalizumab. The skilled person would have concluded that selecting JCV seronegative patients reduced the risk of PML to nearly zero even if "*it meant that most patients could not be treated with natalizumab*" (see document D19, point 11). Further monitoring during treatment as proposed in document D7 was an additional option for a safer treatment.

22. The appellant cited a number of further documents which, in its opinion, indicated to the skilled person that determining JCV antibody status in serum of patients was not conducive to lowering the risk of PML upon natalizumab treatment.

23. The board does not agree. A first set of cited documents relates to PML diagnosis (see document D8E, page 11, penultimate paragraph, and document D28, page 252, right-hand column, last paragraph); JCV antibody status is not useful in this respect as the percentage of seropositive persons in the entire population is too high and "*JCV antibodies levels tend not to increase in the course of the disease*" (see document D8E, supra). Diagnosing PML, however, is different from excluding seropositive patients from treatment and thus avoiding the risk of PML. While doing so might exclude more

patients than necessary, it provides a safer treatment. The second set of cited documents relates to predicting PML several years before the onset of the disease; this is not useful either because it was commonly known that JCV infection and thus seroconversion can arise later in life (see document D21, page 602, left-hand column, last paragraph: "*JCV antibodies in 9 of 14 (64%) initial serum specimens collected from patients who 1 to 9 years later contracted PML*").

24. In conclusion, even after consulting further prior art, the skilled person aiming at a safer treatment would not have been discouraged from following the disclosure of document D7 that "[o]*nly persons infected with JC virus are at risk for PML*" and would have excluded those persons from the treatment with natalizumab.

25. Lastly, the appellant considered the contribution made by the patent to be a "*break-through invention*" because the patent for the first time disclosed using JCV antibody status in serum as a screening marker, providing greatly improved safety for natalizumab treatment. In this context the appellant also argued that the risk of PML for JCV-naive patients was not known before the priority date of the patent.

26. However, there is no evidence for any such "*break-through invention*" in the patent. The only mentions of selecting patients on the basis of a JCV seronegative status are in paragraph [0021] of the patent and claim 20 as filed. The only indirect indication for a safety improvement in JCV seronegative patients is the statement in paragraph [0010] of the patent: "*JC virus (JCV) is the etiological agent of PML and may result from a primary infection or follow reactivation of latent virus*". This, however, is common general

knowledge (see document D8D, page 266, second paragraph). Furthermore, the patent does not contain any risk evaluation for PML in JCV-naive patients, so this argument must also fail.

27. Even if monitoring natalizumab-treated patients were considered a difference from the disclosure of document D7 (see point 10. above), the skilled person would have known that in some populations anti-JCV antibody prevalence continues to rise throughout life (see e.g. document D8B, abstract on page 19), i.e. a primary infection with JCV could also occur during the treatment with natalizumab. Monitoring initially seronegative patients for indicators of PML once the treatment with natalizumab had started was therefore an obvious additional safety measure. Since document D7 already discloses several indicators of PML that should be monitored during treatment with natalizumab (see point 10. above), the skilled person would also have applied this teaching in an obvious manner to the selected seronegative patients.

28. The subject-matter of claim 1 lacks an inventive step (Article 56 EPC).

Main request - claim 1
Inventive step (Article 100(a) EPC and Article 56 EPC)

29. Claim 1 of the main request is broader than claim 1 of auxiliary request 1; it does not include the indication that the "patient is monitored for indicators of progressive multifocal leukoencephalopathy (PML) and if indicators of PML are present, administration of natalizumab is discontinued" (see points I. and IV. above). Therefore, the subject-matter of this claim

lacks inventive step for the same reasons as that of claim 1 of auxiliary request 1.

Auxiliary requests 2 to 9 and 20 to 23 - claim 1
Inventive step (Article 56 EPC)

30. The appellant has not provided any substantial arguments with regard to the inventive step of the subject-matter of claim 1 of these requests. Moreover, document D7 discloses "clinical and/or radiological symptoms of PML", "magnetic resonance imaging (MRI)" (see page 415, right-hand column, last paragraph), "neurological symptoms" (page 415, left-hand column, lines 4 to 5) and "multiple sclerosis" (see page 414, left-hand column, first paragraph), so these do not provide any further differences from the closest prior art.

31. The subject-matter of claim 1 of these requests lacks an inventive step for the same reasons as that of claim 1 of auxiliary request 1.

Auxiliary requests 14 to 17 - claim 1
Inventive step (Article 56 EPC)

32. The appellant indicated that these requests addressed clarity objections; it did not provide any specific arguments with regard to the inventive step of the subject-matter of claim 1.

33. The subject-matter of claim 1 lacks an inventive step for the same reasons as that of claim 1 of auxiliary request 1 (see also point 30. above).

Auxiliary requests 10 to 13, 18, 19, 24 and 25 - claim 1
Inventive step (Article 56 EPC)

34. The appellant argued that the prior art did not suggest monitoring by serially testing for IgG antibodies to JCV in blood of patients treated with natalizumab. The board does not agree because it was common general knowledge that seroconversion can occur during the treatment, e.g. by a new primary infection (see document D8B, abstract on page 19). In view of the disclosure in document D7 that "[o]*nly persons infected with JC virus are at risk for PML*", it was obvious for the skilled person that detecting patients in which seroconversion had occurred during treatment required further monitoring of the JCV IgG status.

35. The subject-matter of claim 1 lacks an inventive step.

Auxiliary requests 20 to 25
Admittance (Article 12(4) and (6) RPBA)

36. In view of the negative finding with regard to inventive step for these requests (see points 30. and 31. and 34.and 35. above), the board considers it unnecessary to provide reasons concerning their admittance.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated