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Datasheet for the decision of 30 March 2022

Case Number: T 2741/19 - 3.3.01

Application Number: 13158951.7

Publication Number: 2645106

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:
Methods for evaluating an immune response to a therapeutic agent

Patent Proprietor:
Biogen MA Inc.

Opponent:
Pharmaceutical Works Polpharma SA

Headword:
Evaluation of immune response to therapeutic protein/BIOGEN

Relevant legal provisions:
RPBA 2020 Art. 13(1)
EPC Art. 123(2), 76(1), 84, 83, 56

Keyword:

Amendment to appeal case
Amendments - allowable (yes)
Divisional application - added subject-matter (no)
Claims - clarity (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:

T 1370/15, T 0608/17, G 0003/14

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2741/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 30 March 2022

Respondent: (Patent Proprietor)	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 (US)
Representative:	Pohlman, Sandra M. df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Appellant: (Opponent)	Pharmaceutical Works Polpharma SA Pelplinska 19 83-200 Starogard Gdanski (PL)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 26 July 2019 concerning maintenance of the European Patent No. 2645106 in amended form**

Composition of the Board:

Chairman	A. Lindner
Members:	T. Sommerfeld
	M. Blasi

Summary of Facts and Submissions

I. European patent 2 645 106 is based on application 13 158 951.7, which was filed as a divisional application in respect of earlier European application 06 749 243.9. The latter had been filed as international application published as WO 2006/107962. The patent is entitled "Methods for evaluating an immune response to a therapeutic agent" and was granted with 21 claims.

II. Opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of inventive step (Article 56 EPC and Article 100(a) EPC), insufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. By an interlocutory decision, the opposition division decided that the patent in amended form on the basis of the fourth auxiliary request containing the set of claims filed with letter of 5 April 2019 met the requirements of the EPC.

The opposition division considered that the claim sets according to the main request and to the first to third auxiliary requests added subject-matter contrary to Article 123(2) and Article 76(1) EPC.

IV. The patent proprietor and the opponent both filed an appeal against the decision of the opposition division.

V. With the statement of grounds of appeal, the patent proprietor requested that the decision be set aside and the patent be maintained in amended form on the basis

of the set of claims of the main request of 26 July 2018 or, alternatively, according to any of the sets of claims of auxiliary requests 1 to 3 of 26 July 2018, or, further alternatively of auxiliary requests 4 to 7 of 5 April 2019, all re-filed with the statement of grounds of appeal. Alternatively, the patent was to be maintained in amended form on the basis of any of the sets of claims of auxiliary requests 8 to 11, filed with the statement of grounds of appeal.

VI. With the statement of grounds of appeal, the opponent requested that the decision be set aside and the patent revoked in its entirety.

VII. With reply to the patent proprietor's grounds of appeal, the opponent submitted new documents D46 and D47 and requested that auxiliary requests 8 to 11 not be admitted into the proceedings and that documents D46 and D47 be admitted.

VIII. By reply to the opponent's grounds of appeal, the patent proprietor maintained its requests as filed with the statement of grounds of appeal. With a later letter dated 3 December 2020, the patent proprietor requested that auxiliary requests 8 to 11 be admitted into the proceedings and documents D46 and D47 not be admitted.

IX. With a further letter dated 15 July 2021, the opponent submitted document D48.

X. By letters dated 26 August 2021 and 26 October 2021, the patent proprietor requested that document D48 and the new submissions based on said document not be admitted into the proceedings. With the latter letter, it further filed sets of claims of new auxiliary

requests 12 to 19, filed "in direct response to the new document D48".

XI. By letter dated 10 December 2021, the opponent requested that document D48 be admitted into the proceedings and provided arguments as to why the new auxiliary requests were not compliant with Article 13(1) RPBA 2020.

XII. Summons to oral proceedings before the board were issued as requested. In its communication pursuant to Article 15(1) RPBA 2020, the board provided a preliminary opinion on some issues, in particular the admission of documents and claim requests into the proceedings.

XIII. By letter dated 22 March 2022, the opponent requested that D48 be admitted into the proceedings as evidence for the skilled person's common general knowledge.

XIV. Oral proceedings before the board took place as scheduled. During the oral proceedings, the patent proprietor stated that auxiliary request 7 was the new main request, auxiliary request 11 was new auxiliary request 1, auxiliary request 15 was new auxiliary request 2 and auxiliary request 19 was new auxiliary request 3. All other claim requests were withdrawn. The patent proprietor then also withdrew the appeal, thus obtaining the procedural role of the respondent in relation to the opponent's appeal. At the end of oral proceedings the chairman announced the board's decision.

Claim 1 of the main request reads:

"1. A method of detecting a clinically significant immune response to natalizumab in a subject, the method comprising determining whether at least two biological samples taken at different time points from a subject that has been administered natalizumab contain at least a clinically significant threshold level of 500 ng/ml in a serum sample of a soluble antibody that binds to natalizumab, wherein said time points are separated by at least 42 days, and wherein the presence of at least the threshold level of the soluble antibody in said at least two samples is indicative of a diminution of efficacy or lack of efficacy of natalizumab."

Claims 2 to 13 are dependent claims and introduce further limitations to the method of claim 1.

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

D4 Calabresi P.A. et al, Neurology 64 (Suppl.1), 2005, A277, abstract S36.002

D5 Roskos L.K. et al., 2005, Measuring Immunity, Chapter 13, 172-186

D6 Rossman H.S., 2004, JMCP, 10 Supplement, S12-S18

D7 Subramanyam M., 2008 Case study Col. II of the series "Biotechnology: Pharmaceutical Aspects" Chapter 10, 173-187

D8 Experimental report of PRA Healthscience, 13 October 2017

D10 Mire-Sluis A.R. et al., J Immunol Methods 289, 2004, 1-16

D13 Calabresi P.A. et al., Neurology 69, 2007, 1391-1403

D20 Pharmacopeia 2013, first supplement, 5732-5743 <Immunogenicity Assays - Design and Validation of Immunoassays to Detect Anti-Drug Antibodies>

D27 Sørensen P.S. et al., Multiple Sclerosis Journal 17(9), 2011, 1074-1078

D42 Print-out of website www.bio-radantibodies.com/tysabri-antibodies-natalizumab.html

D46 Rispens et al., Anal. Biochem. 411, 2011, 271-276

D47 WO 2007/103112

D48 Press release "FDA grants accelerated approval of TYSABRI, formerly antegren, for the treatment of MS", EurekALert!, 23 November 2004

XVI. The submissions of the appellant (opponent), in so far as they are relevant to the present decision, may be summarised as follows:

Admission of documents

Document D48 was submitted after the grounds of appeal or reply thereto but before the summons, so its admission was at the board's discretion, subject to the party's justification. The justification for the late filing was that the document could not be found earlier, despite all due care applied to the preparation of the opposition, and was only found when preparing the opposition for the patent which had been granted on a second divisional application relating to this patent and which was directed to therapeutic uses. According to the criteria for the board's exercise of discretion, namely relevance, current state of the proceedings (before summons), suitability to overcome issues, and procedural economy, the document should be admitted. The aim of the opposition procedure, namely to be able to challenge undeserved patents, should not be jeopardised. The cited passage in the document was

short and easy to understand, so admission of the document into the proceedings would not cause any negative impact on procedural economy. D48 represented common general knowledge and was suitable to solve a number of questions. It disclosed the different patient categories of the patent, namely temporary positive and persistent positive, and that antibody persistency was associated with decreased efficacy. As such, it was *prima facie* relevant. It was well known to the respondent since it was the respondent's own press release, and the respondent had had enough time to react, as it indeed had done. D48 referred to the clinical trials of D4 and complemented this disclosure, thereby reducing the number of issues to be discussed and allowing a streamlined discussion of inventive step. It merely confirmed what the skilled person would have been aware of anyway.

Added subject-matter and clarity

The disclosure at paragraph [0029] of the patent application referred to "500 ng/ml of patient sera" which was not the same as "500 ng/ml in a serum sample" as in the claim. The latter could include diluted serum while the disclosure of paragraph [0029] concerned undiluted serum; the same was true for paragraph [0043]. Paragraph [0057] contemplated undiluted serum. Paragraph [0030] comprised the limitation to serum sample but concerned the biological sample and had no limitation to threshold. Claim 1 was moreover ambiguous in that it covered a serum sample of any dilution and in that it was not clear whether the serum sample was simply the assay matrix or the biological sample, in which case the threshold was not even limiting; dependent claim 11, by specifying that the biological sample was a serum sample, supported the first

interpretation, i.e. that the biological sample in claim 1 was not necessarily a serum sample. This clarity objection was originated from the amendments which did not come from the granted claims because, contrary to the respondent's arguments, granted claim 16 did not provide basis for the amendment "in a serum sample" since the claim was still there as claim 11. As to the feature "time points ... separated by at least 42 days", paragraph [0122] was not a suitable basis because it was part of Example 3, referring back to the assay of Example 2 which was bridging ELISA, such limitations not being in the claim. Moreover Examples 1 and 2 referred to a threshold of serum and paragraph [0119] mentioned "neat (undiluted) serum". The clinically significant threshold was not limited to the sensitivity threshold. Further passages in the description did not provide a basis either. Paragraph [0010] disclosed VLA-4 antibodies in general; paragraph [0044] referred to detection rather than to sensitivity threshold and was not related to natalizumab; paragraph [0038] disclosed a quantitative assay. Paragraph [0033] referred to "about 42 days" and not to "at least 42 days" as in the claim, so at most it could be read as meaning between 42 and 180 days; anyway 42 days was one among several possible time points, therefore requiring selection, and was mentioned in a different context, namely the time interval was not the interval between samples but rather the time when the patient was to be re-classified. The claim involved several selections: threshold level (which was not limited to sensitivity threshold), natalizumab, and 42 days, without there being a pointer to combine them. The examples could not serve as basis because they included other limitations that were not in the claim.

Sufficiency of disclosure

The feature "about 500 ng/ml" was an ill-defined parameter because the term "about" rendered the threshold undefined, thereby hindering the skilled person from carrying out the invention. A precise level of threshold was decisive, as made clear in the patent.

Additionally the claimed method required not only detection but also quantification of neutralising antibodies in order to conclude whether the clinically significant threshold was reached or not. The patent however taught a bridging ELISA assay with optic densitometry values, i.e. a quasi-quantitative assay, but without a real standard sample available (paragraph [0114], Figure 1). It was not apparent how the threshold value had been obtained, nor was it demonstrated that it was equivalent to binding activity. D10, page 2, referred to quasi-quantitative assays, but other assays could be used such as surface plasmon resonance (D20, Table 3 on page 5737). D10 and D5 however demonstrated that different values could be obtained when using different methods. Moreover, the patent did not show that the threshold value in fact had clinical significance.

Moreover, when assuming that the threshold value of claim 1 was in fact a cut-off rather than a sensitivity value, then according to D10's definition of cut-off a level of response had to be defined. D42 demonstrated that different antibodies having different affinities provided different levels of response in an assay, thereby showing that it was essential to have a defined reference antibody (D42, page 7). D8 also showed that the same amount of antibody resulted in different levels of response, depending on the reference antibody used. The examples of the patent used a reference

antibody named 12C4 which was indispensable for establishing the cut-off but was not sufficiently disclosed (column 24, lines 1 to 4) and was not available at the priority date. D46, a statement from an independent source, confirmed that mAb 12C4 was not available and that therefore it was not possible to compare assays. Even if D38 indicated that other assays were available, still their cut-off points would be different.

The patent lacked any disclosure with regard to long-term transient positive patients. D7, D13 and D27 provided evidence that testing for anti-natalizumab antibodies had to be continued for allegedly persistently positive patients for up to two years, since about 50% could revert back to a negative anti-drug serotype, however this teaching was completely missing in the patent.

Inventive step

Document D4 was the closest prior art and differed from the claimed subject-matter in that the following features were not disclosed: the clinically significant threshold of about 500 ng/ml in a serum sample of a natalizumab-binding soluble antibody; and that the presence of at least said threshold of the soluble antibody in two samples was indicative of a clinically significant immune response to natalizumab. The feature that said clinically significant immune response indicated a diminution of efficacy or lack of efficacy of natalizumab was not a distinguishing feature but even if it were, it was nevertheless obvious. In relation to the first distinguishing feature, the technical effect was only to distinguish between presence or absence of anti-natalizumab antibodies,

thereby excluding irrelevant antibodies. Such a threshold was taught in D10, which was common general knowledge, on page 12, left column. As to the second distinguishing feature, the technical effect was that patients were identified that likely had a reduction or lack of efficacy of the therapy. The objective technical problem, in line with the patent's disclosure at column 44, lines 15 to 17, could thus be formulated as providing a method for identifying patients who could experience diminution or lack of therapeutic efficacy with natalizumab. Already in D4 the skilled person was specifically advised to monitor the incidence of antibodies since they caused reduction of efficacy. Therefore, just by following D4, the skilled person would have inevitably identified patients tested positive more than once as having reduced efficacy of therapy. On the other hand, D5, which was common general knowledge, also taught that antibodies against therapeutic proteins resulted in diminution of their efficacy. Also D6, a review article and thus also common general knowledge, discussed the effect of neutralising antibodies to multiple sclerosis treatments. In table 1, D6 listed the clinical consequences, including loss of treatment efficacy, of anti-drug antibodies and on page S16 it referred to "ongoing monitoring", so again testing more than once. This was exactly what D4 did, namely testing every 12 weeks. The link between persistence and lack of efficacy was known from D6, which taught that the antibodies persisted for the majority of the positively tested patients. There was no evidence on file that the skilled person would have stopped using an approved therapeutic antibody if there was only one positive incidence of anti-drug antibody: this was an unsupported allegation by the respondent. The claim just made clear the knowledge of the prior art that

there would be prolonged negative effect when the antibodies were persistently detected. It would then be common sense to discontinue therapy. "Clinically significant immune response" was only in the preamble, without any limitation to about 500 ng/ml, meaning that detection of antibody at any level would be considered as "clinically significant immunity": this was already part of D4.

XVII. The arguments of the respondent (patent proprietor), in so far as they are relevant to the present decision, may be summarised as follows:

Admission of documents

The appellant had not provided an adequate justification for the late filing of D48. Its submission was accompanied by new lines of argumentation that had not been put forward before. D48 moreover did not disclose all features of the claim, so that it would in fact add nothing to the discussion. D48 did not represent common general knowledge and even if it did this would not mean that it could be filed at any time.

Added subject-matter and clarity

Paragraph [0029] last sentence of the application as filed was the basis for the amendment "500 ng/ml of patient sera". The slight change in wording was not a change in content, the correct interpretation being apparent from the whole disclosure, e.g. paragraphs [0012], [0030], [0031], [0043] and [0044]. As to paragraph [0119], while referring to sensitivity, it did not teach away from the clinical threshold. Throughout the whole application it was stated that the

clinically significant threshold was 500 ng/ml, and any other interpretation would not make technical sense and should therefore not be taken into account. Paragraph [0012] referred specifically to 500 ng/ml in a serum sample in the context of natalizumab. From paragraph [0029] and Example 2, the skilled person would understand that this threshold referred to undiluted serum. There could be indeed a clarity issue in view of claim 11, but this was already present in the granted claims so clarity could not be examined. It did not have an impact at all on added subject-matter. There were no multiple selections required, and the examples were a pointer to the claimed combination: natalizumab was not a selection; 500 ng/ml was not a selection but rather the clinically significant threshold; 42 days was the preferred time interval, as clear from the Examples and from paragraph [0033].

Sufficiency of disclosure

The objection concerning the term "about" was in fact a clarity objection. A given ambiguity at the edges of the claim would only lead to an insufficiency of disclosure if it deprived the skilled person from the promise of the invention (T 608/07), and it would be the appellant's burden to prove this by verifiable facts. The patent contained examples on how to carry out a standard ELISA and the skilled person simply had to follow this teaching. Clearly the threshold related to a quasi-quantitative measurement.

As to the measurement, the claim referred to a specific level as threshold, which could be determined by a quasi-quantitative assay such as ELISA. Hence no undue experimentation would be required from the skilled person. D8 only showed that sensitivity could be

affected and that high-affinity antibodies should be selected, which was the same teaching as in the patent. Also D38 used the high-affinity antibody of D8.

The 12C4 antibody was not essential to carry out the invention, as apparent from the patent: paragraph [0062] (column 25, lines 8 to 16) and paragraph [0059]. The claim did not require a control. The patent taught how to carry out the invention and what controls were needed (paragraph [0062]), and the skilled person would be able to set up the assay just following this teaching and using common general knowledge. Natalizumab was known (paragraph [0083]) so the skilled person would be able to produce antibodies against it, in particular high affinity antibodies to replace 12C4 in the assay of paragraph [0112] (paragraph [0110]); any standardised reference sample could be used to calibrate the assay. D8's data were not relevant because they did not show that the 500 ng/ml threshold would be affected. D8 in fact provided evidence that there was a high affinity antibody available, HCA249. Since 12C4 was not essential for performing the invention, D46, which anyway made an incorrect statement concerning 12C4 availability, was of no relevance.

Inventive step

The closest prior art D4 was only an advertisement for an oral presentation at a conference. It provided no data to allow the identification of a clinically significant immune response, not to mention of persistently positive patients. It differed from the claimed subject-matter in three features, as concluded by the opposition division. The technical problem could be formulated as the provision of a method of detecting

anti-natalizumab antibodies in patients undergoing natalizumab treatment that distinguished transient positive patients, for which therapy would be beneficial, from persistent positive patients, for which therapy would no longer be beneficial. The solution was the threshold used in a very specific manner, namely in the measurement of two samples separated by at least 42 days. The solution was not obvious because D4 did not teach any threshold, let alone for the purpose of the claim, and provided no suggestion that this particular read-out was linked to diminution of efficacy. None of D5, D6 or D10 filled the gaps of D4's disclosure. The claim was about finding an antibody response that was associated with reduction or complete loss of efficacy of natalizumab in a patient taking natalizumab, which required at least two positive measurements, as taught in the patent at paragraph [0042] and shown in Example 3, Figures 4 and 5. This teaching was completely absent in the prior art for any therapeutic antibody, let alone for natalizumab. Even if only the claim preamble referred to "clinically significant immune response", the purpose of the method was then further defined in the read-out as being diminution or lack of efficacy.

XVIII. The appellant requested that the decision of the opposition division be set aside and that the patent be revoked in entirety.

The respondent requested that the decision be set aside and the patent be maintained in amended form on the basis of the claims of the main request, filed as auxiliary request 7 with letter dated 5 April 2019 and re-filed with the statement of grounds of appeal, or alternatively, on the basis of the claims of auxiliary request 1, filed as auxiliary request 11 with the

statement of grounds of appeal, or further alternatively, on the basis of the claims of auxiliary requests 2 or 3, filed as auxiliary requests 15 and 19 with letter dated 26 October 2021, respectively.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of documents

Documents D46 and D47

2.1 Documents D46 and D47 have been filed by the appellant with the reply to the grounds of appeal of the respondent (then appellant) and the respondent requested that they not be admitted into the proceedings. Admission of documents D46 and D47 is governed by Article 12(4) RPBA 2007, applicable in the present case pursuant to Article 24(1), (2) and Article 25(2) RPBA 2020. Pursuant to Article 12(4) RPBA 2007 the board has the power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the proceedings before the opposition division even if they comply with Article 12(2) RPBA 2007 and relate to the case under appeal.

2.2 The board decided to admit documents D46 and D47 into the proceedings, in accordance with its preliminary opinion given in the communication pursuant to Article 15(1) RPBA 2020 and based on the considerations set out therein, noting that no further submissions had been presented by the parties on this issue. In view of

the outcome of the present decision, the board sees no need to substantiate this part of the decision.

Document D48

2.3 Document D48 was submitted by the appellant with a later letter, dated 15 July 2021, and the respondent requested that it not be admitted into the proceedings.

2.4 The admission of document D48 is governed by Article 13(1) RPBA 2020, applicable to the present case pursuant to Article 24 RPBA 2020.
Article 13(1) RPBA 2020 stipulates that any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the discretion of the board. Pursuant to Article 13(1) RPBA 2020, the party shall provide reasons for submitting the amendment at this stage of the appeal proceedings and the board shall exercise its discretion in view of, *inter alia*, the current state of the proceedings, the suitability of the amendment to address the issues which were admissibly raised by the other party or the board in appeal proceedings, and whether the amendment is detrimental for procedural economy.

2.5 The appellant did not indicate which allegedly new submissions of the respondent were to be addressed by this new piece of evidence: hence the board does not see how this amendment of case can be suitable to address issues that were admissibly raised by the other party or the board in appeal proceedings. Whatever issues this document might address, these were issues that were present already during the opposition proceedings and as such this document should have been

filed at the latest with the statement of grounds of appeal.

2.6 As justification for the late filing, the appellant indicated that the document was only found during the preparation of the opposition against a patent originating from a divisional application filed in relation to the present patent. The fact that it could not be found easily cannot be accepted as an allowable reason for the document to be admitted at such a late stage of the proceedings. Since D48 was not in the sole possession of the other party but rather was part of the public domain, this argument is not convincing.

2.7 With letter dated 22 March 2022, the appellant argued that D48 was submitted as evidence for the skilled person's common general knowledge at the time. The board notes that this line of argumentation was only submitted after summons for oral proceedings have been issued, and therefore its admission is governed by the provisions of Article 13(2) RPBA 2020, applicable in the present case pursuant to Article 24(1), (2) RPBA 2020.

2.8 Independently of the stage of the proceedings at which the new line of argumentation was submitted, the board disagrees that document D48 can be considered evidence of the skilled person's common general knowledge. It consists of a press release made by the respondent on a very specific subject, namely the FDA approval of TYSABRI (natalizumab) for treatment of multiple sclerosis, and reports on the AFFIRM monotherapy trial for this drug. It is therefore the kind of very specific knowledge on a very specific field that the skilled person may easily become aware of, but which is not part of the skilled person's common general

knowledge, i.e. that knowledge that will normally be found in textbooks or review articles. Hence the conclusions of decision T 1370/15, which relate to common general knowledge, cannot apply here.

2.9 Moreover, even if document D48 were common general knowledge, this does not mean that it could be filed at any time of the proceedings. A piece of evidence of common general knowledge could be filed at a later stage if it serves to back up argumentation that has already been put forward, e.g. to solve a dispute whether facts relied on by a party are common general knowledge or not. This is not the case here because D48 presents new information relative to natalizumab which had not been argued before to be part of the common general knowledge. In fact, as set out above, document D48 has not been filed to further support an existing line of argumentation or as reaction to any new line of argumentation from the other party but rather as a basis for a new objection under inventive step. The board considers that admission of this document adds to the complexity of the case, thus being detrimental to procedural economy.

2.10 The board moreover disagrees that document D48 should be admitted for being *prima facie* relevant, noting that it does not disclose all the features that were missing in the disclosure of the closest prior art D4. Moreover, even if it were regarded as *prima facie* relevant, consideration of D48 would have led to a fresh case on appeal, at a very advanced stage of the proceedings.

2.11 The board thus decided, exercising its discretion pursuant to Article 13(1) RPBA 2020, not to admit document D48 into the proceedings.

Main request

3. Added subject-matter

3.1 Claim 1 of the main request is directed to a method of detecting a clinically significant immune response to natalizumab, the method comprising determining whether at least two biological samples, taken at different time points separated by at least 42 days from a subject that has been administered natalizumab, contain at least a clinically significant threshold level of 500 ng/ml in a serum sample of a soluble antibody that binds natalizumab, wherein the presence of said at least threshold level of soluble antibody in said at least two samples is indicative of a diminution of efficacy or lack of efficacy of natalizumab (for the exact wording of the claim, see section XIV).

3.2 Paragraph [0012] of the application as filed, which is part of the general disclosure of the invention (section "Summary of the invention"), teaches: "According to one aspect of the invention, methods of detecting a clinically significant immune response to a VLA-4 binding antibody in a subject are provided. The methods include determining whether a biological sample from a subject that has been administered a VLA-4 binding antibody contains a clinically significant threshold level of a soluble antibody that binds to the VLA-4 binding antibody, wherein the presence of at least the threshold level of the soluble antibody is indicative of a clinically significant immune response to the VLA-4 binding antibody. In some embodiments, a clinically significant immune response to the VLA-4 binding antibody is indicated by the presence of at least the threshold level of soluble antibody to the

VLA-4 binding antibody in at least two biological samples taken from the subject at different time points. In certain embodiments, the time points are separated by at least one month. In some embodiments, at least the threshold level of soluble antibody that binds to the VLA-4 binding antibody is present in two biological samples taken from the subject at two consecutive time points". Further ahead, it reads that "In some embodiments, the VLA-4 binding antibody is a humanized form of murine antibody mAb 21.6, (e.g., AN100226). In some embodiments, the VLA-4 binding antibody is natalizumab".

3.3 Paragraph [0012] repeatedly refers to a clinically significant threshold level of the antibody but does not define it quantitatively except in a specific embodiment which has features not present in the claim. A quantitative definition is given in paragraph [0029] which teaches that "a 'clinically significant threshold' for an antibody response to a therapeutic protein is at least 2 standard deviations above a control reference level" and then states that "In one embodiment, a clinically significant threshold for anti-natalizumab antibodies is 500 ng/ml of patient sera".

3.4 Hence the board considers that paragraph [0012], read in combination with paragraph [0029], discloses a method with all features of the claimed method except for the time interval between the two measurements being of at least 42 days (in paragraph [0012] at least one month is envisaged) and that the presence of said at least threshold level of soluble antibody in said at least two samples is indicative of a diminution of efficacy or lack of efficacy of natalizumab.

3.5 The feature of the different time points being separated by at least 42 days is disclosed at two instances of the application as filed. Paragraph [0033] teaches the distinction between "transient" and "persistent" positive patients, the latter being patients that test positive for an immune response at two or more time points separated by clinically significant time intervals. As regards the clinically significant time intervals, paragraph [0033] states that they "may be at least one week, one month, one year, or longer. For example, the threshold time interval may be between 30 and 180 days, about 60 days, about 42 days, etc". It then goes on to conclude that "The presence of a persistent immune response may be indicative of a persistently reduced therapeutic efficacy". The second disclosure of the time interval of at least 42 days is in Example 3, paragraph [0122], teaching that "The persistent positive patients had detectable antibodies at two or more time points that were at least 42 days apart".

3.6 The board thus considers that the passage at paragraph [0033] proposes a number of time intervals, among which 42 days, to assess a patient sample for the presence of antibodies against the therapeutic antibody, teaching that the presence of a persistent immune response may be indicative of a persistently reduced therapeutic efficacy. It thus discloses the two features that were missing in paragraph [0012], namely the time interval and the reading-out of the results as being indicative of a reduced therapeutic efficacy. Paragraph [0122] then confirms, on the basis of a screening assay performed on samples of patients according to Examples 1 and 2, and in the context of natalizumab and defining detectable antibodies as being "at a concentration of >0.5 µg/ml" (i.e. 500 ng/ml), that a time interval of

at least 42 days is suitable for identifying persistent positive patients, i.e. those for which natalizumab will have a reduced therapeutic efficacy. As is apparent from paragraph [0120] (Example 2), the screening assay was done with serum samples.

3.7 The board hence comes to the conclusion that claim 1 of the main request finds basis on paragraphs [0012], [0029], [0033] and [0122] of the application as filed.

3.8 The appellant essentially argued that the claim involved several selections, namely the threshold level, natalizumab, and at least 42 days, without there being a pointer to combine them. The feature "500 ng/ml of patient sera" as in paragraph [0029] was not the same as "500 ng/ml in a serum sample" as in the claim, being that the latter could include diluted serum. Moreover the feature "time points separated by at least 42 days" did not have a basis either because paragraph [0122], being part of Example 3, included further limitations (such as the bridging ELISA assay of Example 2) which were not in the claim, and paragraph [0033] referred to "about 42 days" and not "at least 42 days", and this as one among several possible time points and in a different context.

3.9 As to the threshold level, the board notes that the application repeatedly refers to 500 ng/ml as the preferred threshold; in relation to serum samples, it is in fact the only threshold level given (paragraphs [0029], [0043], [0122]). Contrary to the appellant's arguments, the board disagrees that "in a serum sample" in claim 1 can be interpreted as including also diluted samples. If diluted samples were to be used then this would be indicated and the threshold adapted accordingly, as is taught in paragraph [0029].

Regarding natalizumab, this is disclosed throughout the application as filed as the VLA-4 binding antibody which is used as a therapeutic, no other VLA-4 binding antibody being identified. It is thus not a selection from among other alternatives but rather the only element which is specified as being part of the general group of VLA-4 binding antibodies. In any case, it is disclosed at paragraph [0029] in combination with the 500 ng/ml threshold level in serum.

3.10 Finally there might be a selection of at least 42 days among the other possible time intervals listed in paragraph [0033] but in view of this being the only time interval disclosed in the Examples, namely in Example 3 (paragraph [0122]) in the context of a method falling within the claim, this is considered the preferred embodiment. In fact, this represents the only instance in the application as filed where it is clearly stated that a specific time interval (namely at least 42 days) is suitable for identifying persistent positive patients, i.e. those for which natalizumab will have a reduced therapeutic efficacy. While Example 3 might be in the context of specific methods with given limitations which are not in the claim, it is not cited as the basis for the amendment but rather as evidence that the time interval of 42 days would be a preferred one. The board also fails to see an issue in the fact that paragraph [0033] refers to "about 42 days" rather than "at least 42 days": it is clear from the teaching of the application that in order to determine persistent positive patients a minimum time interval between the time points of testing has to be used. So the reference to "about 42 days" in paragraph [0033] would be understood by the skilled person as that 42 days could be used as such a minimum time

interval, meaning that the time interval should be at least 42 days.

3.11 Claim 1 of the main request thus does not add subject-matter within the meaning of Article 123(2) EPC. Since the same passages relied on as basis for the claimed subject-matter are also present in the earlier application as filed (published as WO 2006/107962), claim 1 of the main request does not add subject-matter within the meaning of Article 76(1) EPC either.

3.12 There were no objections under Articles 123(2) and 76(1) EPC directed to the other claims of the main request. The claims of the main request are thus considered to comply with Articles 123(2) and 76(1) EPC.

4. Clarity

4.1 The appellant argued that claim 1 of the main request was unclear because it covered a serum sample of any dilution and it was not apparent whether the serum sample was simply the assay matrix or the biological sample. In view of dependent claim 11, specifying that the biological sample was a serum sample, the first interpretation was pertinent.

4.2 Apart from the fact that the contested limitation to serum sample was already present in the granted claims, namely in claim 16, the board fails to see any lack of clarity deriving from this amendment. First, the skilled person would have no doubts that the threshold level was given only for undiluted samples (see above, point 3.9) and second, it was also clear that if the threshold level is given in relation to a serum sample, then the biological samples taken from the subject must

also be serum samples, at least when they are used as samples for the screening assay (whole blood is drawn from the patient but then centrifuged to obtain the serum). The board agrees that claim 11 of the main request (corresponding to claim 16 as granted) might now be redundant but disagrees that this renders claim 1 unclear.

4.3 Claim 1 of the main request is thus considered to comply with the requirements of Article 84 EPC. No objections under clarity having been raised against the other claims, the board considers that the main request complies with Article 84 EPC.

5. Sufficiency of disclosure

5.1 According to Article 83 EPC, the application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

5.2 The principle underlying the claimed invention is taught in the patent at paragraphs [0027] to [0030], [0032] and [0033] (corresponding to paragraphs [0029] to [0032], [0034] and [0035] of the application as filed). There it is explained that a subject may develop an immunogenic response to a therapeutic protein (e.g. therapeutic antibody such as natalizumab) characterised by increased levels in the subject of one or more antibodies that bind the therapeutic protein. Thus, in the case of natalizumab as therapeutic protein, an immune response may be characterised by the induction of increased levels of soluble antibodies that recognise and bind to natalizumab. The method of the claimed invention thus involves detecting the presence in a sample of a subject that was administered

natalizumab antibodies that bind to natalizumab. According to the claimed invention, a positive test result is determined when the sample contains at least a clinically significant threshold level of binding activity for natalizumab, because the presence of any detectable immune response to natalizumab is not clinically significant: for example, an excessive number of false positives are detected when patients are identified as positive based on an immune response to a therapeutic antibody that is greater than 1.645 standard deviations above a mean level of binding activity present in subjects that have not received the therapeutic antibody. By raising the cut-off level (the level below which a response is considered to be negative) to higher than 1.645 standard deviations above a control reference level, the number of false positives is reduced without affecting the identification of subjects with clinically significant immune responses.

5.3 Hence, a subject's immune response may be classified as negative if samples obtained from the subject do not reach the clinically significant threshold level of antibody response. In contrast, if a subject is identified as positive based on a positive level (a level at or above a clinically significant threshold level) of binding activity in a single assay, the patient may be either a "transient" or a "persistent" positive. A transient positive is a patient who has a positive immune response to the therapeutic antibody for a specified period of time after which the patient becomes negative. In contrast, a persistent positive is a patient who is positive for clinically significant levels of immune response for greater than a specified period of time. Clinically significant time intervals for testing are given in paragraph [0033] of the

application as filed, with examples of threshold time intervals being "between 30 and 180 days, about 60 days, about 42 days, etc". The presence of a transient immune response may be indicative of a transient reduction in therapeutic efficacy while the presence of a persistent immune response may be indicative of a persistently reduced therapeutic efficacy. Accordingly, the presence of a transient or persistent immune response may be clinically relevant and may affect the nature of a therapeutic regimen, since a persistent immune response may necessitate a modification of the subject's therapeutic regimen.

5.4 The principle of the claimed invention is then demonstrated in Example 3, which discloses the results obtained with a screening assay performed on samples from 625 subjects who had been administered natalizumab (paragraph [0122]) and then analyses the effect of antibodies on the rate of relapse of the original disorder in the patients treated. The results, shown in Figures 4 and 5 and discussed in paragraph [0125], demonstrate that from three to six months of treatment the "transient" antibody-positive patients showed diminution in efficacy of the natalizumab treatment while "persistent" antibody-positive patients (i.e. those that had two positive samples taken at least 42 days apart) showed loss of efficiency of natalizumab treatment. From six to twelve months, full efficacy was restored in "transient" antibody-positive patients, but not in "persistent" antibody-positive patients. Accordingly the discrimination between transient antibody-positive and persistent antibody-positive patients is of clinical relevance, as it may have an impact on therapy decisions.

5.5 Assays to detect anti-natalizumab antibodies in patient samples are widely disclosed in the patent application, starting at paragraph [0051], and include well-known assays such as ELISA, radioimmunoassays and surface plasmon resonance. Examples 1 and 2 also provide a disclosure of two such assays, namely a bridging ELISA (paragraph [0114]) and a flow cytometry blocking assay (paragraph [0120]).

5.6 The board thus considers that the claimed subject-matter is sufficiently disclosed in the patent.

5.7 The appellant argued that the claimed subject-matter was insufficiently disclosed for a number of reasons. The clinically significant threshold was defined in the claims in an unclear way, by use of the term "about", and such ill-defined parameter hindered the skilled person from carrying out the invention. The claimed method required quantitation of neutralising antibodies but the patent only taught quasi-quantitative assays such as ELISA, and it was not clear how the clinical threshold was obtained and how it had clinical significance. Moreover, the antibody used as control in the assays of the patent, antibody 12C4, was neither available to the public nor was it sufficiently disclosed, and therefore it was not possible to reproduce the assay. In addition, the patent's disclosure did not allow to distinguish long-term transient positive patients from persistently positive patients.

5.8 The board agrees with the respondent that the objection concerning the use of the term "about" is in fact a clarity objection and therefore is not open to be examined for the claimed subject-matter which is based on the granted claims which already comprised the

feature in which the term "about" appeared (see G 3/14, OJ EPO 2015, A102, Order). Even if measurements just slightly below the threshold value may need further evaluation, the skilled person would still be able to carry out the invention without undue burden. As held in T 608/07, a given ambiguity at the edges of the claim generally does not lead to insufficiency of disclosure.

5.9 Contrary to the appellant's arguments, the board considers that the claimed method does not require absolute quantitation of the detected antibodies but rather just requires that the method establishes whether the antibodies are present above the defined threshold or not. Methods suitable for this purpose are, as stated above, disclosed in the patent and were well known in the prior art (e.g. D10, D20) and the appellant did not show that they would not allow the claimed invention to be carried out. The skilled person would be aware that different assays and different reference antibodies with different affinities could lead to different measurements (as shown in D8 and D42) but this would easily and routinely be solved by calibration using samples with known antibody concentrations, as would be done in any case for methods using new reagents.

5.10 The board also agrees with the respondent that the reference antibody used in the assays of the patent, namely 12C4, is not essential for performing the invention. First, the claims are not restricted to any particular assay, let alone to the use of any specific reference antibody. Any assay will need a reference antibody for standardisation and control but this could be readily obtained or even generated by the skilled person, based on the knowledge of the target protein

natalizumab, the teachings of the patent and common general knowledge. Hence, it is irrelevant whether the 12C4 antibody mentioned in the patent was or is publicly available or not.

5.11 Finally, the board considers that whether the patent lacks any disclosure with regard to long-term transient positive patients or not is outside the scope of the claim which is only directed to identifying patients that have two positive samples taken at least one month apart. The teaching of D7, D13 and D27 that about 50% of the patients identified as having a persistent positive serotype may revert back to a negative anti-drug serotype is therefore irrelevant for the claimed subject-matter.

5.12 The board thus comes to the conclusion that the claims of the main request fulfil Article 83 EPC.

6. Inventive step

6.1 Document D4, a meeting abstract which reports on the safety and tolerability of natalizumab, is the closest prior art. Document D4 reports on the SENTINEL study, a randomised, double-blind, placebo-controlled, multicenter phase III clinical trial in patients with relapsing multiple sclerosis (MS). D4 discloses that patients underwent testing for anti-natalizumab antibodies every 12 weeks using ELISA and states that "the incidence of blocking antibodies to natalizumab and the effects of blocking antibodies on clinical efficacy, MRI efficacy, and safety will be presented".

6.2 D4 differs from the claimed subject-matter in that it does not disclose: "a clinically significant threshold level of 500 ng/ml in a serum sample of a soluble

antibody that binds to natalizumab"; in "at least two biological samples taken at different time points"; and that "the presence of at least the threshold level of the soluble antibody in said at least two samples is indicative of a diminution of efficacy or lack of efficacy of natalizumab". Contrary to the conclusions of the opposition division, however, the board considers that the feature "wherein said time points are separated by at least 42 days" is disclosed in D4, since D4 teaches to test patients every 12 weeks.

6.3 As regards the first difference, the patent application teaches in paragraphs [0043] and [0044] that 500 ng/ml is the clinically significant threshold level which indicates a clinically significant immune response. While these passages refer to "binding activity", paragraph [0122] in Example 3 also gives the same threshold value and renders apparent that concentration and binding activity are used interchangeably. The technical effect linked to this distinguishing feature is thus the identification of a clinically significant threshold.

6.4 Regarding the second distinguishing feature, the following is noted. Again paragraph [0122] in Example 3 teaches that the measurement at two time points allows to distinguish "transiently" positive patients from "persistently" positive patients, being that "persistent positive patients had detectable antibodies at two or more time points that were at least 42 days apart, or at a single time point with no follow-up samples tested". The results of Example 3 are discussed in paragraph [0125]: "From three to six months the 'transient' antibody-positive patients showed diminution in efficacy of the natalizumab treatment. 'Persistent' antibody-positive patients showed lost

[sic] of efficiency of natalizumab treatment. From six to twelve months, full efficacy was restored in 'transient' antibody-positive patients, but not in 'persistent' antibody-positive patients. Accordingly it is important to identify transient antibody-positive patients as a target population for continued VLA-4 binding antibody therapy". Paragraph [0033] on the other hand teaches that "A transient positive is a patient who has a positive immune response to the therapeutic antibody for a specified period of time after which the patient becomes negative. In contrast, a persistent positive is a patient who is positive for clinically significant levels of immune response for greater than a specified period of time". In the same paragraph it is further taught that "Clinically significant time intervals may be at least one week, one month, one year, or longer. For example, the threshold time interval may be between 30 and 180 days, about 60 days, about 42 days, etc" and that "The presence of a transient immune response may be indicative of a transient reduction in therapeutic efficacy" while "The presence of a persistent immune response may be indicative of a persistently reduced therapeutic efficacy. Accordingly, the presence of a transient or persistent immune response may be clinically relevant and may affect the nature of a therapeutic regimen in a subject that is identified as transiently positive or persistently positive. A persistent immune response may necessitate a modification of the subject's therapeutic regimen".

6.5 In agreement with the appellant, the objective technical problem can be formulated as the provision of a method for identifying patients who could experience diminution or lack of therapeutic efficacy with natalizumab and the solution is as claimed. The

question of whether the claimed solution solves the problem or not is not relevant since the purpose of the method is a feature of the claim. In any case, the appellant has not disputed that the solution solves this problem.

6.6 Starting from D4, the skilled person would have been prompted to test serum samples of patients treated with natalizumab for the presence of blocking anti-natalizumab antibodies, would have been able to determine a detection threshold allowing to identify positive samples, and would also have expected that the presence of said antibodies would lead to a decrease of treatment efficacy. However, the skilled person would not have made any distinction between patients for which one sample alone was positive or those for which at least two samples, taken in a time interval of at least 42 days, were positive. From D4 and the remaining prior art (D5, D6, D10), the skilled person would have been prompted to keep on testing (monitoring) for as long as the results were negative but would likely have stopped treatment or at least have considered that there was already diminution of treatment efficacy as soon as a single test turned out positive. In fact, there is nothing in D4 or in the remaining prior art teaching that it is important to distinguish between transient positive (one positive test) and persistent positive patients (two positive tests, taken at least 42 days apart), let alone disclosing a diagnostic method allowing said distinction.

6.7 The board agrees with the appellant that it was common general knowledge at the effective date of claim 1 that development of antibodies against therapeutic proteins such as monoclonal antibodies had an impact in treatment efficacy, possibly resulting in diminution or

even loss of efficacy and that therefore it should be monitored (e.g. D5, page 172, right column, first paragraph; page 173, left column, second paragraph, first sentence; page 175, right column, second sentence; page 176, right column, first sentence of section "Impact in efficacy"; page 183, left column, last paragraph, second and third sentence; D6, page S12, right column; page S16, right column, first and last bullets of section "Implications for Practice"; page S17, left column last sentence; D10, abstract, first three sentences). Also D4 envisages repeated testing ("every 12 weeks") and hints at an effect on clinical efficacy of neutralising anti-natalizumab antibodies. However, as stated above, none of the prior art documents relied upon discloses that it was clinically relevant to evaluate whether the presence of antibodies in the patients' serum was persistent for at least 42 days or not, let alone in the context of natalizumab therapy.

6.8 As pointed out by the appellant, D6 does refer to antibody persistence as being of clinical relevance. However it merely states "An unresolved question with regard to the clinical relevance of NAbs [neutralising antibodies] is how long NAbs persist once they are formed. Available data indicate that once formed, NAbs can persist for several years" (D6, page S16, left column, last paragraph). A similar statement is present in the section "Conclusions" in D6, last two lines of page S16 right column bridging to page S17, line 1: "Another important issue is the persistence of NAbs once they are formed. Available data indicate that once they are formed, NAbs tend to persist for several years". The board disagrees that this disclosure would have led the skilled person to the claimed method. First, it is not related to anti-natalizumab antibodies

and, second and most importantly, it provides no hint on what the clinical significance is and on how long the antibody persistence should be in order to be relevant. In fact, it even appears that one single positive result would already allow the assumption that the antibodies would persist, since D6 suggests that "once they are formed, NAbs tend to persist for several years". This is however contrary to the teaching of the patent that discloses in Example 3 that of the 56 patients that were positive at any time point only 37 patients were "persistently positive", i.e. also positive in a second test (paragraph [0122]).

6.9 The board thus concludes that the claimed subject-matter involves an inventive step. The claims of the main request comply with the requirements of Article 56 EPC.

7. There were no further objections against the claims of the main request. Hence the patent can be maintained in amended form on the basis of the set of claims of the main request.

8. Reimbursement of the respondent's appeal fee at 25%

The respondent withdrew its appeal at the beginning of the oral proceedings before the board. Hence, the respondent's appeal fee is to be reimbursed at 25% pursuant to Rule 103(4)(a) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form with the following claims and a description and drawings to be adapted thereto:

   claims 1 to 13 of the main request, filed as auxiliary request 7 with the statement of grounds of appeal.

3. The respondent's appeal fee is reimbursed at 25%.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated