Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 29 March 2022

Case Number: T 1759/17 - 3.3.01

Application Number: 06749243.9

Publication Number: 1872136

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:
METHODS AND PRODUCTS FOR EVALUATING AN IMMUNE RESPONSE TO A THERAPEUTIC PROTEIN

Patent Proprietor:
Biogen MA Inc.

Opponents:
Urquhart-Dykes & Lord LLP
Pharmaceutical Works Polpharma SA

Headword:
Evaluation of immune response to therapeutic protein/BIOGEN

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

Keyword:

Amendment to appeal case
Amendment after summons - taken into account (no)
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

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1759/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 29 March 2022

Appellant: (Opponent 2)	Pharmaceutical Works Polpharma SA Pelplinska 19 83-200 Starogard Gdanski (PL)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
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)
Party as of right: (Opponent 1)	Urquhart-Dykes & Lord LLP 1 Eversholt Street London Greater London NW1 2DN (GB)
Representative:	Mitchell, Simon James Murgitroyd & Company London Euston House 24 Eversholt Street London NW1 1AD (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 June 2017 concerning maintenance of the European Patent No. 1872136 in amended form**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent EP 1 872 136 is based on application 06 749 243.9, which was filed as international patent application published as WO 2006/107962. The patent is entitled "Methods and products for evaluating an immune response to a therapeutic protein" and was granted with 16 claims.

II. Two oppositions were filed against the granted patent, both opponents 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); additionally, opponent 1 had objections under Article 100(a) EPC in conjunction with Articles 52(2), (3) and 54 EPC and opponent 2 had objections under Article 100(a) in conjunction with Article 53(c) EPC.

III. Opponent 2 (hereinafter, appellant) lodged an appeal against the interlocutory decision of the opposition division, according to which the patent as amended in the form of the main request comprising a set of claims filed on 7 April 2017 met the requirements of the EPC.

The appellant requested that the appealed decision be set aside and the patent revoked in entirety. With the statement of grounds of appeal, the appellant submitted new documents D35 and D36 and raised objections under Articles 123(2), 56 and 83 EPC against the claims considered allowable by the opposition division.

Opponent 1 is party as of right but did not make any submissions as to the substance of the case.

IV. By letter of reply dated 1 March 2018, the patent proprietor (respondent) requested that the appeal be dismissed, i.e. that the patent be maintained as amended in the form of the main request comprising the set of claims of 7 April 2017 or, alternatively, that the patent be maintained in amended form on basis of the set of claims of the first or second auxiliary requests of 7 April 2017. All claim requests were re-filed. Moreover, the respondent submitted new documents D37 to D44 and requested that documents D35 and D36 not be admitted into the proceedings.

V. The appellant submitted a further letter, dated 29 November 2018, thereby filing new documents D45 to D47.

VI. After summons to oral proceedings were issued as requested, the appellant submitted further letters, thereby filing documents D48 and 49 (letter of 8 September 2020) and D50 (letter of 15 July 2021).

VII. The respondent also submitted further letters, thereby requesting that documents D48 and D49 (letter dated 3 December 2020), and document D50 and the new submissions relating to lack of novelty and inventive step based on D50 (letter dated 26 August 2021) not be admitted into the proceedings. By letter dated 26 October 2021, the respondent submitted sets of claims of new auxiliary requests 3 to 8, filed in response to D50.

VIII. By letter dated 10 December 2021, the appellant presented arguments against the admission of auxiliary requests 3 to 8 into the proceedings.

IX. In its communication pursuant to Article 15(1) RPBA 2020, the board provided a preliminary opinion on some issues, in particular on the admission of documents and claim requests into the proceedings.

X. By letter dated 22 March 2022, the appellant requested that D50 be admitted into the proceedings as evidence of common general knowledge and withdrew the objections under added subject-matter in relation to claims 3 and 4 of the main request and auxiliary requests 1 and 2.

XI. In accordance with Rule 115(2) EPC, oral proceedings took place in opponent 1's absence who had informed the board of its non-attendance in advance. At the end of the oral proceedings, the chairman announced the board's decision.

The main request comprises 10 claims. Claim 1 of the main request reads:

"1. A method of detecting a clinically significant immune response to a VLA-4 binding antibody 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 a VLA-4 binding antibody contain at least a clinically significant threshold level of about 500 ng/ml in a serum sample of a soluble antibody that binds to the VLA-4 binding antibody, wherein the presence of at least said threshold level of the soluble antibody in said at least two samples is indicative of a clinically

significant immune response to the VLA-4 binding antibody, wherein said time points are separated by at least one month, and wherein said clinically significant immune response indicates a diminution of efficacy or lack of efficacy of the VLA-4 binding antibody, wherein the VLA-4 binding antibody is nataluzimab."

Claims 2 to 10 are dependent claims and further define the method of claim 1.

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

D3 Calabresi P.A. et al, Neurology 64 (Suppl. 1), 2005, A277, abstract S36.002

D9 Calabresi P.A. et al., Neurology 69, 2007, 1391-1403

D10 Subramanyam M., 2008 Case study Col. II of the series "Biotechnology: Pharmaceutical Aspects" Chapter 10, 173-187

D11 Mire-Sluis A.R. et al., J Immunol Methods 289, 2004, 1-16

D12 Pharmacopeia 2013, first supplement, 5732-5744 <Immunogenicity Assays - Design and Validation of Immunoassays to Detect Anti-Drug Antibodies>

D14 Roskos L.K. et al., 2005, Measuring Immunity, Chapter 13, 172-186

D18 Sørensen P.S. et al., Multiple Sclerosis Journal 17(9), 2011, 1074-1078

D30 Rossman H.S., 2004, JMCP, 10(3) (Suppl S-b), S12-S18

D35 Experimental report of PRA Healthscience, 13 October 2017

D36 Email dated 15 September 2017

D37 van Schie K.A. et al. 2016, J Allergy Clin Immunol 139(3), 1035-1037
D38 Anti-Drug Antibody (ADA) Bridging ELISA - ADA Natalizumab, Bio-Rad protocol
D39 Link J. et al., PLOS One 12(2), 2017, e0170395
D40 Declaration of Dr Lauren Stevenson
D41 Tubridy N. et al., Neurology 53, 1999, 466-472
D42 Vollmer T.L. et al., Multiple Sclerosis 10, 2004, 511-520
D43 WO 2011/044553
D44 Rapid Novor, REmAb™ antibody sequencing webpage
D45 Kromidas S., 1999, "Validierung in der Analytik", 176-181 and 250-251
D46 Print-out of website www.bio-radantibodies.com/tysabri-antibodies-natalizumab.html
D47 Email correspondence between Dr Broekema and Biogen, 9 March 2018
D48 Rispens et al., Anal. Biochem. 411, 2011, 271-276
D49 WO 2007/103112
D50 Press release "FDA grants accelerated approval of TYSABRI, formerly antegren, for the treatment of MS", EurekALert!, 23 November 2004

XIII. Appellant's submissions, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of documents

Documents D48 and D49 were filed in response to the respondent's submissions and were highly relevant as they further confirmed that the antibody 12C4 was not publicly available. They could not have been filed earlier because D48 was only found after a complex and extensive research in the context of opposition proceedings relating to the respondent's owned patent D49.

Document D50 was filed as evidence of the skilled person's common general knowledge before the effective date of the patent. It could not have been filed earlier because it was only retrieved 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 medical uses. Being common general knowledge, it could be filed also at a late stage, as decided in T 1370/15, Catchword. It was directly linked to D3 and served therefore to support the line of argumentation based on D3. It consisted of the respondent's press release concerning the approval of TYSABRI (natalizumab's commercial name) and would have necessarily drawn the attention of the skilled person. While D3 was merely a meeting abstract, D50 complemented D3's abridged disclosure and the skilled person who knew D3 would also have been aware of D50. It was also filed in response to the respondent's challenge at section 38. of the letter of 7 June 2019 that D30's "neutralizing" antibodies would not be the same as "blocking" antibodies. Since D50 was highly relevant, it should be admitted into the proceedings in order to avoid that an unjustified patent monopoly be granted.

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. D11 page 2, referred to quasi-quantitative assays, but other assays could be used such as surface plasmon resonance (D12, Table 3 on page 5737). D11 and D12 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 D11's definition of cut-off a level of response had to be defined. D46 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 (D46, page 7). D35 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 13 to 16) and was not available at the priority date. 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. D9, D10 and D18

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 D3 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 D11, 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 26 to 28, could thus be formulated as providing a method for identifying patients who could experience diminution or lack of therapeutic efficacy with natalizumab. Already in D3 the skilled person was specifically advised to monitor the

incidence of antibodies since they caused reduction of efficacy. Therefore, just by following D3, the skilled person would have inevitably identified patients tested positive more than once as having reduced efficacy of therapy. On the other hand, D14, which was common general knowledge, also taught that antibodies against therapeutic proteins resulted in diminution of therapeutic efficacy. Also D30, a review article and thus also common general knowledge, discussed the effect of neutralising antibodies to multiple sclerosis treatments. In table 1, D30 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 D3 did, namely testing every 12 weeks. The link between antibody persistence and lack of efficacy was known from D30, which taught that the antibodies persisted for the majority of the positively tested patients.

XIV. The respondent's submissions, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of documents

Documents D48 and D49 should not be admitted as they were filed at a very late phase of the appeal proceedings and the appellant had not provided any credible justification for the late filing. Moreover, neither D48 or D49 were *prima facie* relevant, as they did not address the conclusions of the opposition division nor any of the respondent's arguments.

D50 was filed even later and the appellant's submissions did not support that there had been

exceptional circumstances nor cogent reasons within the meaning of Article 13(2) RPBA 2020. D50 was in the public domain since 2004, so there was no reason why it could not have been submitted earlier in the proceedings. It was not common general knowledge, as it did not meet the standards therefor according to the established case law. Moreover it was not *prima facie* relevant. Even when combining D50 with the remaining prior art documents, it still did not disclose the invention.

Sufficiency of disclosure

The objection concerning the term "about" was simply a clarity objection. A given ambiguity at the edges of the claim would only lead to an insufficiency of disclosure of the claimed invention 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 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. D35 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 D35.

The 12C4 antibody was not essential to carry out the invention, as apparent from the patent: paragraph

[0061] (column 25, lines 8 to 16), paragraph [0059]. The claim did not require any particular 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 (paragraph [0112]); any standardised reference sample could be used to calibrate the assay. D35's data were not relevant because they did not show that the 500 ng/ml threshold would be affected. D35 in fact provided evidence that there were high affinity antibodies available.

Inventive step

The closest prior art D3 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 objective 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 one month. The solution was not obvious because D3 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 D11, D14 or D30 filled the gaps of D3'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.

XV. 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 appeal be dismissed, i.e. that the patent be maintained in amended form on basis of the main request with the claims of 7 April 2017, re-filed in appeal with letter of 1 March 2018. Alternatively, it requested that the patent be maintained in amended form on basis of the claims of the first or second auxiliary requests, filed with letter dated 7 April 2017, re-filed in appeal with letter of 1 March 2018, or alternatively, of the claims of auxiliary requests 3 to 8, filed with letter dated 26 October 2021.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of documents

Documents D35 to D44

2.1 Documents D35 to D44 have been filed either with the statement of grounds of appeal (D35, D36) or with the reply thereto (D37 to D44). Their admission 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. According 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 were filed with the statement of grounds of appeal or the reply, comply with Article 12(2) RPBA 2007 and relate to the case under appeal.

2.2 The respondent requested that documents D35 and D36 not be admitted while the appellant has not raised objections against admission of documents D37 to D44.

2.3 The board decided to admit all these documents into the proceedings pursuant to Article 12(4) RPBA 2007, 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. In view of the outcome of the present decision, the board sees no need to substantiate this part of the decision.

Documents D45 to D50

2.4 Documents D45 to D49 have been filed by the appellant after the grounds of appeal and the reply thereto while document D50 was filed even later, after notification of the summons for oral proceedings. The respondent requested that documents D48 to D50, including the related submissions, not be admitted.

2.5 The admission of documents D45 to D49 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. As to document D50, its admission is governed by Article 13(2) RPBA 2020, applicable in the present case pursuant to Article 24(1), (2) RPBA 2020.
Article 13(2) RPBA 2020 stipulates that any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified by cogent reasons by the party concerned.

2.6 As regards documents D45 to D47, the appellant stated (letter of 29 November 2018, page 1, section I) that these documents were filed in direct response to the respondent's reply to grounds of appeal and in particular to the new evidence filed by the respondent. Since there were no objections from the respondent against admission of these documents, the board decided to admit them into the proceedings.

2.7 Documents D48 to D49, on the other hand, were filed with an even later letter, dated 8 September 2020, and the appellant merely indicated in said letter that these new documents were filed in response to the respondent's submission of 7 June 2019, without further explaining which allegedly new submissions of the respondent were to be addressed by the new documents (section I on page 1 of the letter). As noted by the board in its communication pursuant to Article 15(1) RPBA 2020, the respondent had not submitted any new evidence with the letter of 7 June 2019. On page 3, paragraph 11, of its letter of 8 September 2020, the appellant argued that these documents were highly relevant as they "further corroborate the existing line of argument that the antibody 12C4 was not publicly available" and that they could not be filed earlier, D48 having been found only "after a complex and extensive search" in the context of another patent owned by the respondent, namely D49. As stated in the communication pursuant to Article 15(1) RPBA 2020, the board agrees with the respondent that these arguments do not constitute a suitable justification for the late filing of the documents. The appellant did not make further submissions in this respect neither in written nor at oral proceedings.

2.8 The board thus decided, exercising its discretion pursuant to Article 13(1) RPBA 2020, not to admit documents D48 and D49 into the proceedings.

2.9 Finally, document D50 was filed with an even later letter of the appellant, dated 15 July 2021, i.e. after summons to oral proceedings had been issued by the board. Again, the appellant did not indicate which allegedly new submissions of the respondent were to be

addressed by this new piece of evidence. With letter dated 22 March 2022, the appellant argued that D50 was submitted as evidence for the skilled person's common general knowledge at the time. 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.

2.10 The board disagrees that document D50 can be considered evidence of the skilled person's common general knowledge. It consists on 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.

2.11 Moreover, even if document D50 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 D50 presents new information relative to natalizumab which had not been argued before to be part of the common general knowledge.

2.12 Also the fact that it could not be found easily cannot be accepted as an allowable reason to admit the document at such a late stage of the proceedings. Since D50 was not in the sole possession of the other party but rather was part of the public domain, this argument is not convincing.

2.13 Finally, neither the criteria of *prima facie* relevance nor of the need to prevent an "unjustified patent monopoly" play a role for the purposes of Article 13(2) RPBA 2020.

2.14 The board thus considers that there are no exceptional circumstances that could justify admission of document D50 at such a late stage of the proceedings. Hence the board decided not to admit document D50 into the proceedings pursuant to Article 13(2) RPBA 2020.

Main request

3. Sufficiency of disclosure

3.1 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.

3.2 Claim 1 is directed to a method for detecting a clinically significant immune response to natalizumab in a subject that has been administered natalizumab, the method comprising determining whether at least two biological samples taken from the subject at different time points, separated by at least one month, contain at least a clinically significant threshold level of about 500 ng/ml in a serum sample of a soluble antibody

that binds to natalizumab, wherein the presence of at least said threshold level of the soluble antibody in said at least two samples is indicative of a clinically significant immune response to natalizumab, wherein said clinically significant immune response indicates a diminution of efficacy or lack of efficacy of natalizumab.

3.3 The principle underlying the claimed invention is taught in the patent at paragraphs [0028] to [0031] (corresponding to paragraphs [0030] to [0032] 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 recognize and bind to natalizumab. The method of the claimed invention involves detecting the presence of such antibodies in a sample of a subject that was administered 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.

3.4 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's immune response may be either "transient" or "persistent" positive. A transient antibody-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 antibody-positive is a patient who is positive for clinically significant levels of immune response for greater than a specified period of time. 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 can affect the nature of a therapeutic regimen, since a persistent immune response may necessitate a modification of the subject's therapeutic regimen.

3.5 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.

3.6 Assays to detect anti-natalizumab antibodies in patient samples are widely disclosed in the patent, starting at paragraph [0049] (paragraph [0051] in the application as filed), 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]).

3.7 The board thus considers that the claimed subject-matter is sufficiently disclosed in the patent and in the application as filed.

3.8 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.

3.9 In agreement with the respondent, the board considers 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 does generally not lead to insufficiency of disclosure.

3.10 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. D11, D12) 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 D35 and D46) 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.

3.11 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 antibody 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.

3.12 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 D9, D10 and D18 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.

3.13 The board thus concludes that the claims of the main request fulfil Article 83 EPC.

4. Inventive step

4.1 Document D3, a meeting abstract which reports on the safety and tolerability of natalizumab, is the closest prior art. Document D3 reports on the SENTINEL study, a randomised, double-blind, placebo-controlled, multicenter phase III clinical trial in patients with relapsing multiple sclerosis (MS). D3 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".

4.2 D3 differs from the claimed subject-matter in that it does not disclose: the a threshold value of about 500 ng/ml in a serum sample of a soluble antibody that binds to natalizumab; that the presence of at least said threshold level in at least two samples taken at different time points is indicative of a clinically significant immune response to natalizumab; and that said clinically significant immune response indicates 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 one month" is disclosed in D3, since D3 teaches to test patients every 12 weeks.

4.3 As regards the first difference, the patent teaches in paragraphs [0041] and [0042] (corresponding to paragraphs [0043] and [0044] of the application as filed) 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.

4.4 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 [0031] (paragraph [0033] of the application as filed) 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".

4.5 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. 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 this problem was solved.

4.6 Starting from D3, 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 one month, were positive. From D3 and the remaining prior art (D11, D14, D30), 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 D3 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 one month apart), let alone disclosing a diagnostic method allowing said distinction.

4.7 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. D11, abstract, first three sentences; D14, 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; D30, page S12, right column; page S16, right column, first and last bullets of section "Implications for Practice"; page S17, left column last sentence). Also D3 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 one month or not, let alone in the context of natalizumab therapy.

4.8 As pointed out by the appellant, D30 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" (D30, page S16, left column, last paragraph). A similar statement is present in the section "Conclusions" in D30, 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 more 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 D30 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]).

4.9 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.

5. There were no further objections against the claims of the main request, the appellant having withdrawn the initial objections under Article 123(2) EPC against claims 2 and 3. Hence the patent can be maintained as amended according to the main request, as was concluded by the opposition division.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated