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**Datasheet for the decision
of 17 May 2013**

Case Number: T 0734/12 - 3.3.04
Application Number: 04759142.5
Publication Number: 1613350
IPC: A61K 39/395, C07K 16/28
Language of the proceedings: EN

Title of invention:

Therapy of autoimmune disease in a patient with an inadequate response to a TNF-alpha inhibitor

Patent Proprietor:

Genentech, Inc.

Opponents:

Teva Pharmaceutical Industries LTD.
Stada R & D GmbH
Sandoz AG

Headword:

Arthritis patients with an inadequate response to a TNF-alpha inhibitor/GENENTECH, INC.

Relevant legal provisions:

EPC Art. 54, 56, 83, 84, 123(2) (3)

Keyword:

"Added matter, extension of protection (no)"
"Clarity, sufficiency of disclosure, novelty (yes)"
"Inventive step (no)"

Decisions cited:

G 0002/08, T 0019/86, T 0893/90, T 0298/93, T 0233/96,
T 0609/02, T 0986/02, T 1399/04, T 0433/05

Catchword:

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Case Number: T 0734/12 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 17 May 2013

Appellant: Genentech, Inc.
(Patent Proprietor) 1 DNA Way
South San Francisco CA 94080-4990 (US)

Representative: Walton, Seán Malcolm
Mewburn Ellis LLP
33 Gutter Lane
London EC2V 8AS (GB)

Respondent: Teva Pharmaceutical Industries LTD.
(Opponent 1) 5 Basel Street
Petah Tiqva 49131 (IL)

Representative: Baldock, Sharon Claire
Boult Wade Tennant
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT (GB)

Respondent: Stada R & D GmbH
(Opponent 2) Stadastraße 2 - 18
D-61118 Bad Vilbel (DE)

Representative: Neufeind, Regina
Maiwald Patentanwalts GmbH
Elisenhof
Elisenstraße 3
D-80335 München (DE)

Respondent: Sandoz AG
(Opponent 3) Lichtstraße 35
CH-4056 Basel (CH)

Representative: Bohmann, Armin K.
bohmann
Anwaltssozietät
Nymphenburger Straße 1
D-80335 München (DE)

Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted 29 February 2012
revoking European patent No. 1613350 pursuant
to Article 101(3) (b) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Montrone
 R. Morawetz

Summary of Facts and Submissions

- I. The appeal was lodged by the patentee (hereinafter "appellant") against the decision of the opposition division to revoke the European patent No. 1613350 entitled "Therapy of autoimmune disease in a patient with an inadequate response to a TNF-alpha inhibitor" (based on European application number 04759142.5).
- II. The opposition was filed on the grounds in Article 100(a) EPC (lack of novelty, Article 54 EPC and lack of inventive step, Article 56 EPC), Article 100(b) EPC and Article 100(c) EPC.
- III. In its decision under appeal the opposition division decided that the main and auxiliary requests 1 to 3 added subject-matter contrary to the requirements of Article 123(2) EPC. Furthermore, it was decided that the subject-matter of auxiliary request 4 lacked novelty (Article 54 EPC) and auxiliary request 5 was not admitted because it seemed *prima facie* not to overcome the novelty objection raised against the subject-matter of auxiliary request 4 (Rule 116(1) EPC).
- IV. The appeal was filed on 29 March 2012 followed by a statement of grounds of appeal dated 10 May 2012 accompanied by a main request in three versions and auxiliary request 1 to 4 each in three different versions. The appellant also requested acceleration of the appeal proceedings on the basis of three arguments - the possibility of remittal; the suggestion that the decision under appeal which turned on novelty related to an important point of law the resolution of which might take additional time; and the commercial and

medical importance of the patented and approved treatment for which the appellant needs certainty as soon as possible, this being emphasized by the respondents' (alleged) plans to copy the appellant's approved indication and dosing regimen using their biosimilars.

V. The opponent 1, Teva Pharmaceutical Industries Limited, (hereinafter "respondent 1") filed a reply to the statement of the grounds of appeal dated 25 September 2012 and enclosed document (65). As regards the appellant's request for acceleration of the appeal proceedings, respondent 1 replied that, while not convinced that any of the appellant's arguments justified the request, it did not explicitly object to acceleration.

VI. The opponent 2, Stada R & D GmbH, (hereinafter "respondent 2") filed a reply to the statement of the grounds of appeal dated 25 September 2012. As regards acceleration, respondent 2 submitted that it shared an interest in the fast resolution of the appeal proceedings but, if the appeal were to succeed on novelty, it wanted the board to deal also with other issues and not to remit the case to the first instance.

VII. The opponent 3, Sandoz AG, (hereinafter "respondent 3") filed a reply to the statement of the grounds of appeal dated 24 September 2012. Respondent 3 agreed to the acceleration of the appeal proceedings.

VIII. In a communication dated 20 November 2012, the board announced it would expedite the procedure since all the parties had expressed an interest in the early

resolution of the present appeal proceedings and summoned the parties to oral proceedings on 16 May 2013. In an annex to its communication the board gave the following directions for the further conduct of the written proceedings:

- *The appellant may file additional written submissions relating to any issues in the proceedings not made in its statement of grounds of appeal by no later than two months after the deemed date of receipt of this communication. Provided they are confined to such issues and filed in time, those submissions shall be treated as filed pursuant to Article 12(1) (a) and (b) RPBA.*

- *The respondents may each file written submissions in reply to the appellant's additional submissions by no later than two months after the deemed date of receipt of the board's communications notifying those submissions to them. Provided they are confined to replying to the appellant's additional submissions and filed in time, those submissions shall be treated as filed pursuant to Article 12(1) (a) and (b) RPBA.*

- *Any written submissions not complying with 1 and 2 above shall be treated as amendments to a party's case and admissible only pursuant to Article 13 RPBA.*

- *After the time for filing the submissions referred to in 2 above has expired, the board may issue a provisional opinion which may set a short time limit for any written response.*

- *There shall be no extensions of time.*

- IX. With its letter of 29 January 2013 the appellant filed a replacement auxiliary request 4 in three versions and additional documents (67) to (71).
- X. Respondent 2 in response filed further observations in its letter dated 21 March 2013.
- XI. Respondent 1 in its letter of 11 April 2013 presented further arguments, requested that documents (67) to (71) be not admitted into the proceedings, and enclosed additional documents (72) and (73).
- XII. Respondent 3 in its letter of 11 April 2013 filed further arguments and requested that documents (68) to (70) be not admitted into the proceedings.
- XIII. In a communication of 19 April 2013 the board informed the parties about the order in which it intended to discuss the various issues at the oral proceedings and that arrangements had been made to continue the oral proceedings on 17 May 2013 if necessary.
- XIV. Oral proceedings were held before the board on 16 and 17 May 2013. At the oral proceedings the board held that the main request and auxiliary requests 1 to 3 in all three versions filed with the statement of the grounds of appeal dated 10 May 2012 and the replacement auxiliary request 4 in all three version filed with the appellant's letter dated 29 January 2013 did not fulfil the requirements of Article 123(2) EPC. The appellant then filed a new main request and auxiliary requests 1 to 4, each in two versions. The board decided that one

version of these new requests did not comply with the requirements of Article 123(2) EPC. The remaining new main request and auxiliary requests 1 to 4 then replaced all previous requests which were withdrawn.

- Claim 1 of the main request reads:

"1. Use of an unconjugated antibody which is rituximab in the manufacture of a medicament for treating rheumatoid arthritis by intravenous administration of two doses of antibody of 1000mg to a human who experiences an inadequate response to a TNF α -inhibitor, wherein the first dose is administered on day 1 of treatment and the second dose on day 15."

- Claim 1 of auxiliary request 1 reads:

"1. Use of an unconjugated antibody which is rituximab in the manufacture of a medicament for treating rheumatoid arthritis by intravenous administration of two doses of antibody of 1000mg to a human who experiences an inadequate response to previous or current treatment with a TNF α -inhibitor because of inadequate efficacy, wherein the first dose is administered on day 1 of treatment and the second dose on day 15."

- Claim 1 of auxiliary request 2 reads:

"1. Use of an unconjugated antibody which is rituximab in the manufacture of a medicament for treating rheumatoid arthritis by intravenous administration of two doses of antibody of 1000mg

to a human who experiences an inadequate response to previous or current treatment with a TNF α -inhibitor because of inadequate efficacy, defined as a human who continues to have active rheumatoid arthritis following previous or current treatment with the TNF α -inhibitor, wherein the first dose is administered on day 1 of treatment and the second dose on day 15."

- Claim 1 of auxiliary request 3 reads:

"1. Use of an unconjugated antibody which is rituximab in the manufacture of a medicament for treating rheumatoid arthritis by intravenous administration of two doses of antibody of 1000mg to a human who experiences an inadequate response to previous or current treatment with a TNF α -inhibitor because of inadequate efficacy, defined as a human who has active disease activity after 1 month or 3 months of therapy with the TNF α -inhibitor, wherein the first dose is administered on day 1 of treatment and the second dose on day 15."

- Claim 1 of auxiliary request 4 reads:

"1. Use of an unconjugated antibody which is rituximab in the manufacture of a medicament for treating rheumatoid arthritis by intravenous administration of two doses of antibody of 1000mg to a human who experiences an inadequate response to a TNF α -inhibitor, defined as a human who has received previous or current treatment with etanercept for \geq 3 months at 25 mg twice a week,

with at least 4 infusions of infliximab at ≥ 3 mg/kg, and/or with adalimumab and wherein said human has:

- (i) swollen joint count ≥ 8 , of 66 joint count, and tender joint count ≥ 8 , of 68 joint count;
- (ii) either CRP ≥ 15 mg/L or ESR ≥ 28 mm/h; and/or
- (iii) radiographic evidence of at least one joint with definite erosion attributable to rheumatoid arthritis, the at least one joint being any joint of the hands, wrists or feet with the exception of the DIP joints of the hands,

wherein the first dose is administered on day 1 of treatment and the second dose on day 15."

XV. The documents referred to in the present decision are:

- D7: Edwards, 2002, Arth. & Rheum. 46(9): S197
- D8: Tuscano, 2002, Annual Scientific Meeting of the American College of Rheumatology, Oct 24-29; New Orleans, LA, p3420
- D10: Press Release of Genentech dated October 28, 2002
- D13: Arthritis Research Campaign (arc) press release, October 2002
- D14: MabThera, EU Summary of Product Characteristics (SmPC) (2010)
- D16: Cohen et al., 2006, Arth. & Rheum. 54(9): 2793-2806
- D25: Gremillion & van Vollenhoven, 1998, Postgraduate Medicine 103:103-123
- D26: First Declaration of R.F. van Vollenhoven
- D33: Berinstein et al., 1998, Ann. Oncol., 9: 995-1001

- D35: Rituximab (Rituxan®), United States Prescribing Information (USPI), October 2003
- D36: Furst et al., 1989, J. Rheumatol., 16: 313-329
- D37: St. Clair et al., 2002, Arth. & Rheum. 46(6): 1451-1459
- D38: Infliximab (Remicade®), United States Prescribing Information (USPI), June 2002
- D40: Declaration of Dr. Jeffrey N. Siegel, M.D.
- D44: Seymour et al., 2001, Br. J. Clin. Pharmacol., 51: 201- 208
- D57: Hueber et al., 2009, Arth. Res. Ther. 11(3): 1-13
- D58: Koczan et al., 2008, Arth. Res. Ther. 10(3): 1-10
- D62: Third declaration of R.F. van Vollenhoven
- D65: Declaration of Dr. Fang Xie
- D67: Declaration of Dr. Peter Treasure
- D68: Simsek, 2012, Bulletin of the NYU Hospital for Joint Diseases, 70(3): 187-190
- D69: Chen, 2011, Arthritis Research & Therapy, 13:R126, 1-10
- D70: Alzabin, 2012, Ann. Rheum. Dis., 71: 1741-1748
- D71: van de Veerdonk, 2011, Arth. & Rheum., 63(6): 1507-1516
- D72: Second declaration of Dr. Fang Xie
- D73: Appendix to Dr. Fang Xie's second declaration

XVI. The appellant's arguments, as far as they are relevant for the present decision, may be summarised as follows:

Admissibility of main request and auxiliary requests 1 to 4 filed at oral proceedings

- The requests were filed in reaction to the board's view that the previous requests did not comply with Article 123(2) EPC. The new requests were narrower in scope

than those previous requests, they did not contain any unexpected amendments, and they were readily understandable for the respondents. Accordingly they should be admitted by the board in its discretion pursuant to Article 13 RPBA.

Admissibility of documents (67) to (71)

- Document (67) is a declaration from a professional clinical statistician provided in direct answer to respondent 1's document (65) which criticised earlier evidence of the appellant. Since document (65) invited a reply, this was provided in document (67) which should therefore be admissible.

- Documents (68), (69) and (70) demonstrate further that rheumatoid arthritis (RA) patients who experience an inadequate response to a TNF α -inhibitor have a distinct pathological or physiological status, in particular increased Th17 cell numbers and IL-17. Document (71) confirms that there is a functional relationship between the therapy in such patients conferred by administration of rituximab and their distinct pathological or physiological status, in particular rituximab causes reduction in Th17 cells and IL-17 in the patients. These documents further support novelty.

- The appellant was not aware of any of these documents when filing its grounds of appeal. The review document (68) was published after the grounds of appeal were filed and refers to document (69), which was published earlier but the appellant was not aware of it when filing the grounds. Document (70) is very similar to document (69) in its findings and was published only

days before the grounds were filed. Document (71) is very pertinent in that it confirms the functional relationship mentioned above.

Novelty (Article 54 EPC)

- The disclosure of document (10) was not detrimental to the novelty of the subject-matter of claims 1 and 2 of all claim requests since it disclosed neither a RA patient sub-group experiencing an inadequate response to a TNF α -inhibitor nor the successful treatment of this particular patient group.

Inventive Step (Article 56 EPC)

- The closest prior art was represented by document (8) disclosing the treatment of TNF α -inhibitor refractory RA patients by an escalating dosage regimen using rituximab as therapeutic agent.
- Starting from document (8) as closest prior art, the technical difference was the provision of a successful treatment of the patient group claimed.
- The objective technical problem was the provision of a treatment allowing the successful treatment of TNF α -inhibitor refractory RA patients with rituximab. The problem was solved by providing the clinical protocol of the patent in suit.
- The solution should be considered non-obvious over the cited prior art since the skilled person starting from document (8) would, in view of the unsatisfactory results obtained, have selected higher rituximab

dosages given more often and over a longer period of time in accordance with dosage regimens used for methotrexate (MTX) and TNF α -inhibitors in the treatment of RA patients or for rituximab in the treatment of Non-Hodgkin's Lymphoma (NHL) (see documents (33), abstract, (35), table 2, (36) and (37) both abstracts). The skilled person would not have considered document (10) since it is only a press release and moreover discloses a reduced dose of rituximab given less frequently which was contrary to the established practice for comparable drugs as mentioned above.

XVII. The respondent's arguments, as far as they are relevant for the present decision, can be summarised as follows:

Admissibility of main request and auxiliary requests 1 to 4 filed at oral proceedings

- The requests were late-filed and did not overcome the objections under Article 123(2) EPC upheld by the board in relation to the appellant's previous requests. The board should therefore refuse to admit the requests under Article 13 RPBA.

Admissibility of documents (67) to (71)

- Respondent 1 argued that all these documents should be disregarded because they were not submitted in due time in accordance with Article 114(2) EPC. The board's directions explicitly stated in its Directions for Expedited Proceedings that the appellant should file additional written submissions relating to any issues in the proceedings not made in its statement of grounds of appeal, the appellant having only addressed the

issue of novelty over document (10) in its statement of grounds.

The introduction of further evidence in support of novelty contravenes Article 12(2) RPBA which requires the grounds of appeal to contain a party's complete case. As regards the appellant's argument that it was not aware of any of documents (68) to (71) when filing its grounds of appeal on 9 May 2012, document (69), to which document (68) refers, and document (71) were publicly available in 2011.

- Respondent 3 argued that documents (68) to (70) do not have any bearing on the issue of lack of novelty and therefore should not be admitted.

Novelty (Article 54 EPC)

- The subject-matter of claims 1 and 2 of all requests lacked novelty over the disclosure of document (10) since an RA patient experiencing an inadequate response to a TNF α -inhibitor neither defined a pathological or physiological status nor was a particular beneficial therapeutic effect associated with the selection of the patient group claimed contrary to the established case law, in particular decision T 233/96 of 4 May 2000.

Inventive Step (Article 56 EPC)

- Document (10) should be considered the closest prior art since it aimed at the same purpose, namely the treatment of RA, and had the most relevant technical features in common.

- The objective technical problem to be solved was the provision of a treatment for an alternative RA patient group.
- The solution, namely the selection of TNF α -inhibitor refractory RA patients, was considered to be obvious in view of document (8) disclosing the successful treatment of this patient group by administering rituximab albeit with a different dosage regimen.

XVIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or one of auxiliary requests 1 to 4 all filed during the oral proceedings.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. In view of its decision on Article 56 EPC (see below) the board will not provide an extensive reasoning why it held the subject-matter of the main request and auxiliary requests 1 to 4 to meet the requirements of Articles 123(2), 123(3) and 84 EPC.

Procedural matters

Expedited proceedings

2. In the board's opinion the reasons advanced by the appellant for accelerating the appeal proceedings (see section IV above) did not in themselves justify acceleration. As regards possible remittal, many

appeals arise from decisions on one point only and thus include the issue whether or not to remit if successful. As regards a possibly important point of law, the board was not satisfied that there was such a point but, even if there was, it did not accept that this would necessarily require additional time, there being already a considerable case law on the question which criteria define a new patient subgroup.

3. As regards the appellant's commercial significance argument, many if not all patentees consider their patents to be of commercial significance and, if that were a criterion for acceleration, it would be impossible for the board to decide which are of such importance as to merit acceleration and which not. That is doubtless one reason why acceleration has been acknowledged as appropriate when infringement proceedings are threatened or pending. The appellant however alleged only planned copying by use of biosimilars and not that any of the opponents had infringed or were about to infringe, let alone that infringement proceedings were pending or even contemplated.

4. However, it was clear to the board that there was a substantial measure of agreement between the parties on an early resolution of the issues (see sections IV to VII above): of the four parties, three agreed to acceleration and the fourth did not object. Such agreement is not only relatively rare but must be seen against the background of the current length of the board's list of cases. While it gives the board no pleasure to say so, four years is currently the average time taken to dispose of pending appeals and parties

filing new appeals are now being warned routinely by the board that they may expect their appeals to occupy four years. If in a minority of cases, both or most or all parties are agreed that their case should be expedited, then the board should be willing to do so. If this means that such a minority of cases thereby overtake the majority of cases where there is no such agreement, and that the list of pending cases is thereby divided into two lists of expedited non-expedited cases, then that will be a proper reflection of party disposition. Further, the public has an interest in the early resolution of disputes as to the existence or extent of a patent monopoly and it is logical to assume that a dispute in which all the parties agree to an early resolution are those which may affect the public most.

5. Thus the board considered that in all the circumstances of the case the interests of the parties and of the public would best be served by an expedited procedure and by dealing with all outstanding issues in the present appeal proceedings. Accordingly oral proceedings were appointed for an early date in the board's schedule and, since not all parties had presented written submissions on all outstanding issues, the board made directions intended to bring all the parties' submissions into the same state of preparedness (see section VIII above).

Admissibility of main request and auxiliary requests 1 to 4 filed at oral proceedings

6. While, as the respondents argued, these requests were late-filed, inasmuch as they were only filed during the

oral proceedings, the board agrees with the appellant that they were narrower in scope than the appellant's previous requests, they did not contain any unexpected amendments, and they were readily understandable for the respondents. Moreover they were clearly filed only as a result of the announcement of the board's view that it agreed with the respondents' objections under Article 123(2) EPC to the previous requests. Thus the new requests introduced no complexity, were to be expected in the current state of the proceedings, did not affect procedural economy, and did not raise issues which the board and the respondents could not deal with without an adjournment. Accordingly, in exercising its discretion under Article 13(1) and (3) RPBA, the board saw no reason not to admit these requests into the proceedings.

Admissibility of documents (67) to (71)

7. Respondent 1's document (65), a declaration of Dr. Fang Xie, a medical statistician, begins by describing the statistical analysis in the appellant's document (61), the third declaration of Dr. van Vollenhoven, a professor of clinical therapy research, as "entirely misleading" and the conclusions drawn by the appellant from that analysis as "based on a misinterpretation of the data available". There follow three pages of explanation why Dr. Xie considers Dr. van Vollenhoven's analysis to be incorrect and concludes with the statement that, for the reasons she gives, she considers his analysis "not at all convincing". That document was filed with respondent 1's reply to the statement of grounds of appeal. While, as respondent 1 argues, it is correct

that the statement of grounds of appeal and reply should each contain a party's complete case (Article 12(2) RPBA), and further correct that in the present case the board's directions were intended to prevent the appellant adding to its written case on novelty when providing written submissions on other issues, it would be unconscionable to allow respondent 1's reliance on those procedural formalities to shut out of the proceedings the appellant's evidence in response to document (65), namely document (67), the declaration of Dr. Treasure, another medical statistician. Parties producing evidence containing allegations such as "misleading", "misinterpretation" and "not at all convincing" are, as the appellant argued, inviting evidence in reply. In the board's view, they are also inviting the consideration of the admissibility of such reply evidence under Article 13 RPBA. In the exercise of its discretion under that Article, the board had no hesitation in admitting document (67).

8. The position as regards documents (68) to (71) is quite different. The appellant's submissions of 29 January 2013 consisted of a letter and an annex described as follows:

"This letter is filed pursuant to Item I of the Board's Directions, providing the [appellant's] comments on issues not made in our statement of grounds of appeal dated 10 May 2012. The main part of this letter addresses inventive step and sufficiency of disclosure.... In the Annex we provide comments strictly in reply to the submissions made by the Respondents on alleged added subject-matter and on novelty. Our case on these matters is set out in our

statement of grounds of appeal. The Respondents have responded with various additional points and the annex is confined to matters in reply... We believe this submission is in accordance with the Board's directions and the Rules of Procedure of the Boards of Appeal."

It was however clear, on the face of that statement of the appellant, that it had not complied with the board's directions. It did not confine its submissions to issues not raised in its grounds of appeal, although it did confine its letter to such issues. The annex to the letter was, as the statement quoted above candidly admits, a reply to the respondents' replies. In the ordinary course, that would fall to be admitted in the board's discretion under Article 13(1) RPBA and, in the present case, that was clearly underlined by item 3 of the directions. Considering documents (68) to (71), which were filed as part of the annexed submissions, the board found them no more relevant than the appellant's previous evidence and, for this reason alone, decided not to admit them into the proceedings.

Substantive matters

Article 123(2) and (3) EPC

Main Request

9. The board is satisfied that the subject-matter of claims 1 and 2 finds a basis in claim 12 as originally filed in combination with the disclosure on page 41, lines 7, 8, 14 and 15 and page 44, line 8 of the application as filed.

10. Moreover, the board is satisfied that claims 1 and 2 of the main request comply with the requirements of Article 123(3) EPC. Claim 1 in combination with claim 5 as granted refers to the second medical use of intravenously administered CD20 antibodies for the treatment of mammals suffering from rheumatoid arthritis (RA) and experiencing an inadequate response to a TNF α -inhibitor. The subject-matter of claims 1 and 2 of the main request is, however, restricted to rituximab as a single specific anti-CD20 antibody and to humans as patients. Hence the overall scope of protection conferred by claims 1 and 2 is more restricted than claim 1 of the patent as granted and fulfils the requirements of Article 123(3) EPC.

Auxiliary Request 1

11. The board is satisfied that the wording introduced by amendment "patients who experience an inadequate response to a previous or current treatment with a TNF α -inhibitor because of inadequate efficacy" finds a basis on page 6, last paragraph of the application as filed. The requirements of Article 123(2) EPC are thus fulfilled.
12. The subject-matter of auxiliary request 1 is even more restricted than the subject-matter of the main request. Consequently, in the light of the arguments of point 10, *supra*, the board holds the requirements of Article 123(3) EPC as met.

The same holds good for auxiliary requests 2, 3 and 4 considered in points 13 to 15 below.

Auxiliary Request 2

13. The board notes that the wording introduced by the amendment "patients who experience an inadequate response to previous or current treatment with a TNF α -inhibitor because of inadequate efficacy, defined as a human who continues to have active rheumatoid arthritis following previous or current treatment with the TNF α -inhibitor" finds a basis on page 7, lines 6 and 7 in combination with the disclosure on page 6, last paragraph of the application as filed. Hence the subject-matter of claims 1 and 2 fulfils the requirements of Article 123(2) EPC.

Auxiliary Request 3

14. The board is satisfied that the amended feature "patients who experience an inadequate response to previous or current treatment with a TNF α -inhibitor because of inadequate efficacy, defined as a human who has active disease activity after 1 month or 3 months of therapy with the TNF α -inhibitor" finds a basis on page 7, lines 6 to 8 in combination with the disclosure on page 6, last paragraph of the application as filed. Hence the subject-matter of claims 1 and 2 fulfils the requirements of Article 123(2) EPC.

Auxiliary Request 4

15. The board notes that amended claims 1 and 2 find a basis on page 43, line 22 to page 44, line 4 (example 1) of the application as filed. The omission of the previously included features "as determined by the central reading site" and "because of toxicity or

inadequate efficacy" does not contravene the requirements of Article 123(2) EPC, as the first relates to a mere indication of a blinded study and therefore has no technical meaning (see document (16), page 2796, col. 1, second paragraph) and the second feature is covered by the term "inadequate response". These deletions do not therefore result in any extension beyond the content of the application as originally filed. Hence, the subject-matter of claims 1 and 2 complies with the requirements of Article 123(2) EPC.

Article 84 EPC - Main and Auxiliary Requests 1 to 4

16. The board considers the amendments introduced into the subject-matter of claims 1 and 2 of the main request and of auxiliary requests 1 to 4 to be clear in view of the definitions given for "inadequate response to a TNF α -inhibitor" on page 6, last paragraph and page 7, lines 6 to 8 of the application as filed. The same applies to the parameters used for further defining the patient group according to claims 1 and 2 of auxiliary request 4 as given in example 1, starting on page 43, line 34 to page 44, line 4 of the application as filed. Hence, the subject-matter of claims 1 and 2 of all the requests is clear and fulfils the requirements of Article 84 EPC.

Article 83 EPC - Main and Auxiliary Requests 1 to 4

17. The subject-matter of independent claims 1 and 2 of all five requests relates to a second medical use of rituximab for the treatment of RA by the intravenous administration of two doses of rituximab of 1000mg to a

- human who experiences an inadequate response to a TNF α -inhibitor, wherein the first dose is administered on day 1 of treatment and the second dose on day 15.
18. The case law has interpreted the provisions of Article 83 EPC as met, in relation to claims to a second medical use, if (i) the disclosure content of the application or the common general knowledge at the relevant date enables the skilled person to produce the compounds as claimed and (ii) the claimed treatment can be achieved in a reliable and reproducible manner (Case Law of the Boards of Appeal, 6th edition 2010, II.A.4.2, 7th paragraph). It follows from this that either the application must provide suitable evidence for the claimed therapeutic effect or it must be derivable from the prior art.
19. In the present case this means that the suitability of rituximab for the treatment of patients suffering from RA who experience an inadequate response to TNF α -inhibitors by intravenously administering two doses of rituximab of 1000mg on day 1 of treatment and the second dose on day 15 has to be credible to the skilled person either from the teaching of the application as filed or from the common general knowledge at the relevant date (see decisions T 609/02 of 27 October 2004 or T 0433/05 of 14 June 2007).
20. The board notes, when evaluating the quality of evidence provided in the application as filed, that it contains a clinical protocol for the claimed rituximab dosage regimen in treating TNF α -inhibitor refractory RA patients in example 1 which does not go beyond the mere statement that the patients treated **will** show a

beneficial clinical response defined at least as an ACR20 response (see page 45, last paragraph in combination with page 44, lines 16 to 18 of the application as filed). However, experimental or clinical data supporting this statement are not provided. Hence, the disclosure content of the application is not sufficient for providing a credible support that rituximab is suitable for the treatment as claimed in all five requests.

21. However, the board also observes that it is undisputed by the parties that at the relevant date rituximab was a well known commercially available antibody destroying B cells by binding to the CD20 molecule on the surface of the cells. Moreover, it was common general knowledge at the time that TNF α -inhibitors act independently from rituximab in treating RA patients by using a completely different and independent mode of action (see document (38), page 2, first paragraph; document (7), abstract 446, first paragraph). Consequently, the skilled person knew that any failure regarding a previous TNF α -inhibitor treatment of RA patients does not automatically result in an ineffective rituximab treatment of the same patient group. Moreover, any toxicity or unwanted side-effects experienced by a patient in response to the use of a TNF α -inhibitor cannot be transferred to patients taking rituximab since both agents detect different target molecules (TNF α versus CD20) and are chemically distinct. Additionally, the skilled person was aware of document (10) which discloses the successful treatment of **all 31** methotrexate (MTX) refractory RA patients by the administration of the claimed rituximab dosage regimen (see document (10), page 1, third and fourth paragraph).

However, the board observes that document (10) is silent on any TNF α -inhibitor refractory RA patients including their successful treatment with rituximab in the claimed dosage regimen. But it is undisputed by all the parties that it belonged to the common general knowledge before the priority date that **30 to 40% of the total group of RA patients** are inherently TNF α -inhibitor refractory (see document (26), point 7; document (44), page 201, fifth paragraph). The skilled person being aware of this high percentage and looking at a patient group size of 31 individuals as disclosed in document (10) would consider it statistically plausible that at least some of these patients are inherently TNF α -inhibitor refractory.

Taking all these facts from the prior art together, the board is satisfied that a treatment of the patient group by rituximab in the dosage regimen according to claims 1 and 2 of the main and auxiliary requests 1 to 4 can be plausibly achieved and that the subject-matter meets the requirements of Article 83 EPC.

Article 54 - Main and Auxiliary Requests 1 to 4

22. The board observes that document (10), a press release published by the appellant discloses the use of rituximab in a dose of 1000mg administered on day 1 and day 15 for treating MTX refractory RA in human patients (see page 1, paragraphs 1 to 4).

The document neither refers to RA patients responding inadequately to a TNF α -inhibitor nor does it disclose the successful treatment of these patients by administering rituximab.

23. The opposition division referred in its decision to decisions T 233/96 of 4 May 2000, T 1399/04 of 25 October 2006 and G 0002/08 published in OJ EPO, 2010, 456. It acknowledged that the patient group according to the patent in suit differed from the group disclosed in document (10) by the feature "a human who experiences an inadequate response to a TNF α -inhibitor". However, this feature was considered either to be too vague and thus resulting in a large or even complete overlap with the patient group of document (10) or to lack a common physiological and pathological status in view of the manifold and divergent reasons causing it. Furthermore, the selection of the patient group was considered to be arbitrary since it did not particularly profit from the rituximab treatment as shown in post published document (14) (see page 24, lines 8 and 9) and therefore lacked a technical effect. Moreover, the criteria for its selection seemed rather to be based on economic or public health rather than on technical reasons. Novelty was thus denied. The respondents used in essence the same arguments.
24. According to the established case law of the Boards of Appeal, the use of the same compound in the treatment of the same disease for a particular group of subjects, could nevertheless represent a novel therapeutic application, provided that it is carried out on a new group of subjects which is distinguished from the former by its **physiological or pathological** status (see decisions T 19/86, OJ EPO 1989, 24, point 8 of the reasons; T 893/90 of 22 July 1993, point 4.2 of the reasons; T 1399/04 of 25 October 2006, point 35 of the reasons).

25. The RA patient group according to claims 1 and 2 of the main request is defined by experiencing an inadequate response to a TNF α -inhibitor. The term "inadequate response" covers toxicity, in the sense of negative side-effects and/or inadequate efficacy in response to treatment with a TNF α -inhibitor (see page 6, last paragraph to page 7, first paragraph of the application as filed). The board notes that it is undisputed by all the parties that it belonged to the common general knowledge before the priority date that 30 to 40% of all RA patients are TNF α -inhibitor inadequate responders (see point 21, above). From this fact alone it follows that the patient group of document (10) cannot be identical to the patient group of the patent in suit because, as indicated by the opposition division, it only discloses RA patients being MTX non-responders. The ability to select a RA patient sub-group based on their inadequate response to TNF α -inhibitor is derived from physiological differences between this group and the remaining group of RA patients which is confirmed by document (57) (see page 1, abstract) and document (58) (see page 1, abstract). Moreover, the pathological status of this selected RA patient sub-group will be different because they either suffer from TNF α -inhibitor induced side-effects and/or have an altered degree of RA in comparison to the group of document (10).

26. Hence, the RA patient group of claims 1 and 2 of the main request is distinguishable from the patient group of document (10) by its **physiological and pathological** status and consequently, according to the established case law of the Boards of Appeal (cf. decisions

T 1399/04, T 19/86 and T 893/90, above) represents a new therapeutic application. Therefore, the argumentation of the opposition division or the respondents, that the criteria for the selection of the patient group are merely based on economic and public health reasons, is not accepted.

27. In addition to the above arguments, the board notes that document (10) is not only silent regarding any RA patients responding inadequately to TNF α -inhibitor but also it does not disclose the successful treatment of this patient sub-group by administering rituximab. Consequently, document (10) does not disclose the technical effect underlying the subject-matter of claims 1 and 2.
28. In view of these arguments the board does not need to further examine the statistical data provided by the parties which either support or deny the presence of a particular beneficial therapeutic effect for the RA sub-group as claimed (see documents (62), (65), (67) or (72)) since the only relevant prior art (document (10)) does not disclose such an effect.
29. Hence, the subject-matter of claims 1 and 2 of the main request is novel and fulfils the requirements of Article 54 EPC.
30. The subject-matter of independent claims 1 and 2 of the auxiliary requests 1 to 4 differs from claims 1 and 2 of the main request in that the patient group is further defined by either restricting it to TNF α -inhibitor non-responders (auxiliary requests 1 to 3) or by characterising the phenotype of the RA patients

after having been treated by three specific TNF α -inhibitors (auxiliary request 4).

31. Accordingly, the same considerations apply *mutatis mutandis* to the subject-matter of claims 1 and 2 of auxiliary requests 1 to 4.

Article 56 EPC - Main Request

32. The only two claims of the main request are second medical use claims in either the Swiss-type claim format or the purpose-related claim format according to Article 54(5) EPC. Except for that formal difference the two claims relate to the same subject-matter namely the use of an unconjugated rituximab in treating rheumatoid arthritis by the intravenous administration of two doses of antibody of 1000mg to a human who experiences an inadequate response to a TNF α -inhibitor, wherein the first dose is administered on day 1 of the treatment and the second dose on day 15.

Closest prior art

33. The closest prior art is generally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical features in common, i.e. requiring the minimum of structural modifications. This is not different with respect to the claims currently under consideration, i.e. second medical use claims (see decision T 986/02 of 21 October 2004, points 5 and 6 of the reasons). Ideally, the purpose or objective should be something already mentioned in this prior art document as a goal worth

achieving (see decision T 298/93 of 19 December 1996, point 2.2.2 of the reasons).

34. The board takes the view that the invention underlying the patent in suit serves the purpose of providing a treatment for rheumatoid arthritis (RA) in human patients who experience an inadequate response to a TNF α -inhibitor. In the light of the criteria for identifying the closest prior art as elaborated by the Boards of Appeal, a document aiming at the same purpose, i.e. treatment of RA in human patients who experience an inadequate response to a TNF α -inhibitor, is considered to be the most appropriate starting point for the objective assessment of an inventive step following the criteria of the "problem and solution approach".
35. Document (10), a document proposed by the respondents as closest prior art, describes the treatment of RA in human patients with unconjugated rituximab in the dosage regimen as referred to in claims 1 and 2 but is silent on any RA patients who experience an inadequate response to a TNF α -inhibitor. Document (8) however, mentions the successful treatment of infliximab-refractory RA in human patients with rituximab in a different dosage regimen from that presently claimed. Infliximab is a known TNF α -inhibitor (see e.g. paragraph 14 of the patent in suit).
36. The board disagrees with the respondents and considers document (8) to be directed to the same purpose or effect as the invention, namely the treatment of the same RA patient group and thus to be treated as the

closest prior art for assessing inventive step (Article 56 EPC).

Problem and Solution

37. In view of the absence of any data provided in the patent in suit demonstrating an improvement over the treatment results known from document (8), the board considers that the objective technical problem underlying the present invention must be seen in the provision of an alternative treatment of RA patients with an inadequate response to TNF α -inhibitors.

38. The question of whether or not the claimed solution, i.e. the subject-matter of claims 1 and 2, can be regarded as a solution to the problem formulated above does not arise in view of the language of these claims (see also point 21, above).

Obviousness

39. It remains to be assessed whether or not the subject-matter of claims 1 and 2 is obvious.

40. Document (8) reports a small study of nine RA patients of which seven were evaluable. These patients received an escalating dose of rituximab starting with 100mg in week 1, followed by an administration of 375mg/m² in week two and receiving a further 500mg/m² in weeks three and four. It is indicated that all patients treated had improved joint scores, reductions in Rheumatoid Factor (RF) and C-Reactive Protein (CRP) levels and three even met the criteria for an ACR20 response. Moreover, the document concludes that the data obtained support the

- hypothesis that rituximab is a promising agent for treating patients with disease-modifying anti-rheumatic drug and infliximab-refractory RA (see abstract).
41. The skilled person looking at document (8) would (i) learn that rituximab is in principle suitable for the treatment of TNF α -inhibitor refractory RA patients and (ii) that the treatment used requires further improvement in view of the rather unsatisfactory clinical effects obtained. Consequently, the board considers that the report of document (8) provides the motivation for the skilled person to deviate from the proposed treatment.
42. Document (10) is a press release of Genentech, Roche and IDEC Pharmaceuticals Corp. summarising interim data of 122 patients of a phase II study of MTX refractory RA patients who were treated with two 1000mg rituximab doses given two weeks apart. The study is silent on any TNF α -inhibitor refractory RA patients. In a group of 31 patients receiving rituximab in the same dosage regimen as claimed, 58% of the patients experienced an ACR20 response, 32% an even better ACR50 response and 13% a further improved ACR70 response at 24 weeks post treatment (see document (10), page 1, third and fourth paragraph). The board notes that this press release was commented by document (13), in which the Arthritis Research Campaign (ARC), a British medical research charity, interpreted the data of the clinical study as "revolutionary" with regard to the treatment results obtained and indicated further advantages of the therapy, namely the only twofold administration two weeks apart which unlike the anti-TNF α inhibitor RA therapies does not require permanent medication (see

document (13), page 1, paragraphs 1 to 3 and 5, page 2, paragraph 8). In view of document (13), the board regards the appellant's arguments (see document (40), point 39) that the skilled person would not consider "press releases", such as document (10) as not convincing. The skilled person represented by an organisation such as ARC, obviously closely followed press releases of pharmaceutical companies in particular, if they related to very positive results of clinical studies as in the case of document (10).

43. The board further observes that it is undisputed by the appellant that it belonged to the common general knowledge of the skilled person before the priority date of the patent in suit that 30 to 40% of all RA patients are inherently TNF α -inhibitor non-responders (see document (26), point 7; document (44), page 201, fifth paragraph).

44. In the board's view, the skilled person taking together the disclosures of documents (8) and (10) would have been motivated to use the dosage regimen of administering twice 1000mg rituximab two weeks apart for the treatment of RA patients that are TNF α -inhibitor refractory in view of the significant therapeutic improvements achieved for RA patients being MTX refractory. Even if this meant a reduced overall dose of rituximab given less frequently and at a shorter time period in comparison to document (8). The board furthermore observes that **all** of the RA patients treated according to the dosage regimen of document (10) showed at least an ACR20 response (see, page 1, fourth paragraph).

45. In this respect the board notes that the appellant's argumentation as to why the skilled person would not have been motivated to apply the dosage regimen of document (10) to the TNF α -inhibitor refractory RA patient group is not persuasive. The appellant argued that the skilled person confronted with the unsatisfactory therapy results of document (8) would rather increase the rituximab doses and would administer it over a longer period of time in view of the trend at the relevant date to use increased doses of medicaments to improve their efficacy (see e.g. use of increased doses of MTX to increase its efficacy (document (36), title and abstract); increased doses of TNF α -inhibitors in treating RA patients (see document (37), abstract) and increased doses of rituximab to improve treatment of Non-Hodgkin's Lymphoma patients (NHL) (see document (33), abstract and page 999, column 1; document (35), table 2).
46. However, the board observes that (i) MTX and TNF α -inhibitors are in substance completely different therapeutic agents than rituximab using moreover a separate and independent mode of action (see for TNF α -inhibitors e.g. document (38), page 2, first paragraph; for MTX: see document (25), table 1 on page 116). Thus, any clinical effects obtained by administering an escalating dose of these agents are not transferable to rituximab. Secondly, (ii) the treatment of NHL refers to the acute, life-threatening disease leukaemia, whereas RA is a slowly progressing, chronic autoimmune disease. Again, the board has no reason to conclude that any results obtained by treating NHL with rituximab of a certain dose can be extrapolated to the treatment of RA because the diseases are fundamentally

different irrespective of the fact that the underlying mechanism of action, namely the depletion of B cells by rituximab, is the same for both diseases.

47. Consequently, the board is of the view that there was no teaching in the prior art which would have restrained the skilled person from administering the dosage regimen of document (10) to the TNF α -inhibitor refractory RA patient group. On the contrary, the successful treatment of **all** RA patients with the dosage regimen of document (10) offered the skilled person a high expectation of success by treating that group with rituximab given as a single dose of 1000mg given two weeks apart. This was particularly so, since the skilled person at the priority date was aware of the fact that any unsuccessful treatment of RA patients with TNF α -inhibitors had no influence on a later rituximab treatment because of the separate and independent mode of action of the two different therapeutic agents (see point 21, above). In addition, it belonged to the common general knowledge of the skilled person at the relevant date that 30 to 40% of all RA patients were known to be inherently TNF α -inhibitor non-responders. In view of this high percentage it was highly probable that in a group of 31 individuals which were all successfully treated by the dosage regimen as claimed (see document (10), page 1, fourth paragraph) at least some would be also TNF α -inhibitor inadequate responders in addition to being MTX refractory (see point 21, above). The skilled person would have therefore combined the teaching of documents (8) and (10) and would have arrived at the subject-matter of claims 1 and 2 of the main request in

an obvious manner without exerting any inventive skill, contrary to the requirements of Article 56 EPC.

Article 56 EPC - Auxiliary Requests 1 to 4

48. The subject-matter of independent claims 1 and 2 of auxiliary requests 1 to 4 differs from claims 1 and 2 of the main request in that the patient group is further defined by either restricting it to TNF α -inhibitor non-responders (auxiliary requests 1 to 3) or by characterising the phenotype of the RA patients after having been treated with three specific TNF α -inhibitors (auxiliary request 4).
49. The board observes that this restriction of the patient group to either true non-responders or by defining the phenotype of the RA patients in response to the treatment of three specific TNF α -inhibitors has no influence on the selection of the closest prior art or the formulation of the objective technical problem to be solved because of the absence of any data provided in the patent in suit demonstrating an improvement over the treatment results known from document (8).
50. The problem to be solved therefore remains the same as that formulated for the main request (see point 37, *supra*).
51. Consequently, the same considerations of obviousness relating to the subject-matter of the main request apply *mutatis mutandis* to the subject-matter of claims 1 and 2 of auxiliary requests 1 to 4 (see points 39 to 47, above).

52. Hence, the subject-matter of claims 1 and 2 of auxiliary requests 1 to 4 is not inventive and does not fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

P. Cremona

C. Rennie-Smith