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Datasheet for the decision of 20 April 2021

Case Number: T 2168/17 - 3.3.04

Application Number: 10009416.8

Publication Number: 2272868

IPC: C07K16/00, A61K39/395

Language of the proceedings: EN

Title of invention:
Combination therapy for B cell disorders

Patent Proprietor:
Genentech, Inc.

Opponent:
GlaxoSmithKline Intellectual Property Management Limited

Headword:
Combination therapy 2/GENENTECH

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

Keyword:
Late-filed request - admitted (yes)
Inventive step - (no)

Decisions cited:

Catchword:
-

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Case Number: T 2168/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 April 2021

Appellant: (Opponent)	GlaxoSmithKline Intellectual Property Management Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Hitchcock, Lucy Rose GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 August 2017 concerning maintenance of the European Patent No. 2272868 in amended form.**

Composition of the Board:

Chairman	B. Claes
Members:	B. Rutz
	P. de Heij

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the opposition division's interlocutory decision that European patent No. 2 272 868 (hereinafter "the patent") in the form of the main request complied with the requirements of the EPC. The patent is entitled "*Combination therapy for B cell disorders*".

Claim 1 of the main request reads:

"1. A CD20 binding antibody and a BLyS antagonist as a combination for use in a method of alleviating a B-cell regulated autoimmune disorder, the method comprising administering to a patient suffering from the disorder a therapeutically effective amount of the CD20 binding antibody and of the BLyS antagonist."

II. The opposition proceedings were based on the grounds in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.

III. In the statement of grounds of appeal, the appellant argued, *inter alia*, that the subject-matter of claim 1 of the main request and of all the auxiliary requests lacked an inventive step.

IV. With their reply to the appeal, the patent proprietor (respondent) filed sets of claims of a main request (identical to the set of claims of the main request on which the decision under appeal was based, see section I) and auxiliary requests 1 and 2 (identical to auxiliary requests 1 and 2 in the opposition proceedings), 3 (newly submitted), 4 (identical to

auxiliary request 3 in the opposition proceedings) and 5 to 11 (newly submitted).

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request.

Claim 1 of auxiliary requests 2 and 4 reads (difference from claim 1 of the main request underlined):

"1. A CD20 binding antibody and a BLyS antagonist as a combination for use in a method of alleviating a B-cell regulated autoimmune disorder, the method comprising administering to a patient suffering from the disorder a therapeutically effective amount of the CD20 binding antibody and of the BLyS antagonist, wherein the BLyS antagonist is an anti-BLyS antibody."

Claim 1 of auxiliary requests 3 and 5 reads (difference from claim 1 of the main request underlined):

"1. A CD20 binding antibody and a BLyS antagonist as a combination for use in a method of alleviating a B-cell regulated autoimmune disorder, the method comprising administering to a patient suffering from the disorder a therapeutically effective amount of the CD20 binding antibody and of the BLyS antagonist, wherein the BLyS antagonist is an anti-BLyS antibody and wherein the anti-BLyS antibody partially or fully blocks BR3 interaction with a BLyS polypeptide."

Claim 1 of auxiliary requests 6 and 7 differs from claim 1 of the main request and of auxiliary request 1 by the addition of "wherein the autoimmune disorder is systemic lupus erythematosus (SLE) or lupus".

Claim 1 of auxiliary requests 8 and 10 differs from claim 1 of auxiliary requests 2 and 4 by the addition of "wherein the autoimmune disorder is systemic lupus erythematosus (SLE) or lupus".

Claim 1 of auxiliary requests 9 and 11 differs from claim 1 of auxiliary requests 3 and 5 by the addition of "wherein the autoimmune disorder is systemic lupus erythematosus (SLE) or lupus".

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

VI. Oral proceedings before the board took place in the form of a videoconference with the parties' consent. At the end of the oral proceedings, the chair announced the board's decision.

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

E1 WO 03/014294

E8 Edwards J. C. W. et al., "*B-lymphocyte depletion therapy in rheumatoid arthritis and other autoimmune disorders*", Biochemical Society Transactions 30(4), 2002, 824-828.

E9 Mackay F. et al., "*BAFF and APRIL: A tutorial on B Cell Survival*", Annual Review Immunology 21, 2003, 231-264.

E18 Silverman G. J. and Weisman S., "*Rituximab Therapy and Autoimmune Disorders*", Arthritis & Rheumatism 48(6), 2003, 1484-92.

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

Main request and auxiliary request 1

Inventive step (Article 56 EPC) - claim 1

The disclosure in document E18 represented the closest prior art and described in detail rituximab (CD20-binding antibody) monotherapy in autoimmune disease. It furthermore disclosed which B cell subtypes were responsible for the autoimmune disease and would need depleting in order for the treatment to be therapeutic (page 1489, last paragraph).

The difference between the disclosure in document E18 and the claimed subject-matter was the combination of a CD20-binding antibody with a BLyS antagonist, and the objective technical problem was to provide an improved therapy for B cell regulated autoimmune diseases.

Document E18 itself already suggested that this problem could be solved by using agents that blocked BLyS/BAFF/zTNF4, all being synonyms (see page 1490, second column, middle paragraph).

The skilled person also knew of a suitable agent from document E1, which disclosed in particular in Example 7 the effects of a BLyS antagonist, immunoadhesin BR3-Fc, in an *in vivo* lupus model and concluded that "*BR3-Fc*

treatment blocked production of autoantibodies by B cells in the lupus mice and enhanced survival by blocking TALL-1 [BLyS] *function* in vivo". Document E1 also proposed that a BLyS antagonist could be combined with a CD20-binding antibody (see page 112, lines 7 to 8).

The argument that the skilled person would not consult document E1 when starting from the disclosure in document E18 representing the closest prior art because document E9 taught away from targeting the BAFF/BLyS system failed because document E9 in fact concluded that the BAFF system was well studied and "*yielded a clear and relatively unambiguous picture*", which was "*unusual in immunology*" (see page 253, last paragraph).

The person skilled in the art would thus supplement document E18's rituximab with the BLyS antagonist known from document E1 to improve B cell depletion in order to improve the known therapy for B cell regulated autoimmune diseases.

The claim lacked an inventive step over the disclosure in document E18 when considered alone or when combined with the disclosure in document E1.

Auxiliary request 2

Inventive step (Article 56 EPC) - claim 1

The additional feature "wherein the BLyS antagonist is an anti-BLyS antibody" did not result in inventive subject-matter because document E1 taught that "*TALL-1 antagonists ... contemplated for use further include anti-TALL-1 antibodies*" (page 11, lines 5 to 6 (TALL-1 being a synonym of BLyS: see page 1, line 22)). The

view that all TALL-1 antagonists disclosed in document E1 were equivalent was confirmed on page 47, lines 3 to 13, which defined "*TALL-1 antagonists*" as "*any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of TALL-1*" and listed a number of antagonists, including BR3-receptor immunoadhesins and BLyS (TALL-1) antibodies.

The skilled person would thus have considered an anti-BLyS antibody as an obvious alternative to BR3-Fc, which was used in Example 7 of document E1 and shown to be effective against lupus.

Auxiliary request 3

Admittance (Article 12(4) RPBA 2007)

The request should not be admittedinto the appeal proceedings.

Inventive step (Article 56 EPC)

The additional feature "wherein the BLyS antagonist is an anti-BLyS antibody and wherein the anti-BLyS antibody partially or fully blocks BR3 interaction with a BLyS polypeptide" did not contribute to inventive step because document E1 taught that "*anti-TALL-1* [BLyS] *antibodies ... are capable of blocking or reducing binding of the respective ligands to the TACIs or BR3 receptors.*" (page 11, lines 6 to 8). The term "BR3 receptors" was synonymous with "BR3" (see document E1, page 15, lines 19 to 21). Moreover, Example 7 in document E1 showed that interfering with the BR3-BLyS interaction by way of a soluble BR3-Fc immunoadhesin was effective in treating lupus.

Auxiliary requests 4 to 11

Inventive step (Article 56 EPC)

No comments were submitted with regard to inventive step.

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

Main request and auxiliary request 1

Inventive step (Article 56 EPC) - claim 1

The disclosure in document E18 represented the closest prior art. The difference between the claimed subject-matter and the disclosure of document E18 was the combination of a CD20-binding antibody and a BLyS antagonist for use in a method of alleviating a B cell regulated autoimmune disorder. This combined administration depleted all B cell subsets (see paragraphs [0271], [0272] and [0297] of the patent).

The technical effect achieved by the invention was improved depletion of all B cell subsets. Indeed, based on the data presented in the patent, the claimed combination of agents resulted in an improvement in B cell depletion not only in terms of the number of B cells, but also in terms of the types of B cells depleted which made it possible to alleviate B cell regulated disorders.

The objective technical problem could thus be formulated as the provision of an improved treatment of B cell regulated autoimmune diseases.

Document E18 speculated that the efficacy of rituximab treatment for patients with autoimmune diseases might be improved by the addition of a second agent. It listed various alternative approaches, one of which was the use of an agent that blocked the BLyS/BAFF/zTNF4 system, but it did not specifically mention a BLyS antagonist as recited in the claims. No pointer was however disclosed to the particular selection of this approach compared with any of the various other approaches hypothesised in document E18. Document E18 (as well as document E1 and the other cited documents) did not suggest that this approach actually improved depletion of B cells when used in combination with rituximab. The disclosure in document E18 was therefore highly speculative.

Documents E8 and E9, scientific review articles published shortly before the priority date, taught away from the claimed invention, i.e. the additional use of BLyS antagonists. Document E8 raised questions as to the relevance of anti-DNA antibodies (see page 827, left-hand column, second-to-last paragraph) and plasma cells (see page 827, right-hand column, second paragraph). Document E9 further cast doubts on the need for BAFF (BLyS) for *in vivo* survival of B cells, in particular plasma cells (see page 242, second paragraph) and the involvement of BAFF (BLyS) in the germinal centre reaction (see page 244, second paragraph).

The person skilled in the art would thus not have arrived at the claimed combination of agents and reasonably expected that their administration would improve B cell depletion, both in terms of number and types of B cells depleted, in order to improve treatment of B cell regulated autoimmune diseases.

Therefore the claimed subject-matter involved an inventive step.

Auxiliary request 2

Inventive step (Article 56 EPC)

Starting from the disclosure in document E18 representing the closest prior art, the skilled person, even if considering document E1, would not have combined a CD20-binding antibody with an anti-BLyS antibody because only results for a BR3-Fc immunoadhesin were disclosed in document E1 (Example 7).

Auxiliary request 3

Admittance (Article 12(4) RPBA 2007)

The request should be admitted into the proceedings.

Inventive step (Article 56 EPC)

Blocking the interaction between BLyS and BR3 was not disclosed in any of the cited documents and was therefore a further feature which contributed to the claimed subject-matter not being obvious to the skilled person, and thus being inventive.

Auxiliary requests 4 to 11

Inventive step (Article 56 EPC)

No comments were submitted with regard to inventive step.

X. The appellant requested that the decision under appeal be set aside and the patent be revoked. They also requested that auxiliary request 3 be not admitted into the proceedings.

The respondent's requests, as far as relevant to the decision, were that the appeal be dismissed (i.e. that the patent be maintained on the basis of the main request considered by the opposition division to comply with the EPC), or alternatively that the decision under appeal be set aside and the patent be maintained on the basis of the set of claims of one of auxiliary requests 1 to 11, all filed with the reply to the statement of grounds of appeal. They also requested that auxiliary requests 3 and 5 to 11 be admitted into the proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request and auxiliary request 1

Inventive step (Article 56 EPC) - claim 1

Closest prior art and objective technical problem

2. A combination of a CD20-binding antibody (such as rituximab) and a BLyS antagonist for use in a method of alleviating a B cell regulated autoimmune disorder (e.g. systemic lupus erythematosus (SLE)) is claimed (see sections I and IV).

3. Both parties agreed that the disclosure in document E18 represented the closest prior art. The board sees no reason to deviate from this.

4. Document E18 discloses the treatment of B cell regulated autoimmune diseases (e.g. systemic lupus erythematosus (SLE) and rheumatoid arthritis) with rituximab (a CD20-binding antibody). In a section entitled "*Rituximab for SLE*", document E18 further discloses that administering rituximab reduces the levels of peripheral B cells in SLE patients (see page 1487, right-hand column, second-to-last paragraph: "*rituximab often resulted in significant depletion in the levels of peripheral B cells*"; and page 1488, left-hand column, lines 1 to 3: "*After treatment, the levels of B lymphocytes were depleted in the peripheral blood for at least 3-16 months*"). Moreover, with regard to rheumatoid arthritis patients, document E18 discloses that following rituximab treatment "[a]*ll patients had significant depletion of peripheral B cells*" (see page 1488, right-hand column, last paragraph).

5. Document E18 accordingly teaches that depletion of B cells is relevant to treating autoimmune diseases such as SLE and rheumatoid arthritis, and that this can be achieved, at least partially, by administering rituximab.

6. The claimed subject-matter differs from the therapy disclosed in document E18 in that the CD20-binding antibody (rituximab) is used in combination with a BLyS antagonist (such as a BR3 immunoadhesin or an anti-BLyS antibody) for treating autoimmune diseases.

7. Example 4 of the patent demonstrates improved B cell depletion for the combination referred to in the claim

as compared with a CD20-binding antibody (rituximab) or a BLyS antagonist (BR3-Fc) alone. In particular Figures 29 to 31 show the reduction of B220+ splenocytes and of CD21 and CD23 positive subpopulations, representing MZ and T2/FO cells, in response to the combination treatment. During oral proceedings the parties agreed that B220 was a marker for "all B cells". The board thus concludes that improved B cell depletion is achieved at least in the spleen as manifested by the reduced numbers and types of B cells. Improved B cell depletion will translate into improved treatment of B cell regulated autoimmune disorders.

8. The objective technical problem can thus be formulated, as it was by the parties, as providing an improved method for alleviating B cell regulated autoimmune disorders.

Obviousness

9. Document E18 discloses that upon treatment with rituximab in SLE patients levels of autoantibodies to native DNA and complement were not affected (page 1487, right-hand column, second-to-last paragraph). It further states that: "*rituximab as a single agent may not be adequate for the treatment of diseases resulting from the production of pathogenic autoantibodies, since it is likely that the dominant cellular source of disease-associated autoantibodies, especially IgG antibodies, are* [sic] *plasma cells that do not bear CD20 (Figure 2).*" (see page 1489, right-hand column, last paragraph). Document E18 therefore teaches that the B cell depletion achieved by rituximab treatment was not sufficient to treat diseases resulting from the production of pathogenic autoantibodies.

10. It is proposed in document E18 that "*the optimal treatment of diseases that have autoantibody mediated pathology may require a regimen that also affects plasma cells*" (page 1489, right-hand column, last paragraph) and that "*the long-term goal of therapy should be to eliminate all components of the disease-associated autoimmune process, including the offending autoreactive B cells, plasma cells, and memory cells*" (page 1490, left-hand column, first paragraph).

11. Document E18 offers a potential solution to this problem by suggesting that "*the efficacy of rituximab treatments for patients with autoimmune diseases may be improved by the addition of second agents*" and that "*it may be desirable to utilize agents that block the recently discovered BLyS/BAFF/zTNF4 system (for review, see ref. 47), to interfere with these potent survival signals directed toward membrane-associated receptors on peripheral B cells*" (page 1490, right-hand column, middle paragraph). It was commonly known that BLyS played an important role in the survival of B cells (see background section of the patent, page 2, paragraph [0005]: "*BLyS (also known as BAFF, TALL-1, THANK, TNFSF13B, or zTNF4) is a member of the TNF1 ligand superfamily that is essential for B cell survival and maturation*" and "*signaling through BR3 mediates the B cell survival functions of BLyS*"). Document E18 accordingly further teaches that a solution to the ineffective treatment of autoimmune diseases with rituximab might be to combine it with a BLyS blocking agent to interfere with the survival signals on peripheral B cells.

12. Accordingly and in summary, document E18 discloses that (i) B cell depletion with rituximab was not sufficient

for treating diseases resulting from the production of pathogenic autoantibodies, such as SLE, that (ii) further B cell types, including plasma cells, should be depleted and that (iii) the BLyS system of survival signals was a potential target for achieving this.

13. Document E1 discloses specific solutions for blocking the BLyS system by stating, for example, that "*BR3 receptor immunoadhesins ... preferably block or reduce the respective receptor binding or activation by TALL-1* [BLyS] *ligand*" and "*anti-TALL-1* [BLyS] *antibodies ... are capable of blocking or reducing binding of the respective ligands to the ... BR3 receptors*" (page 10, line 39 to page 11, line 8).

14. The skilled person aiming at improving the treatment of B cell regulated autoimmune disorders would thus have consulted document E1, which *inter alia* relates to BR3 and its ligand BLyS ("*also referred to as TALL-1, BAFF or THANK*", see document E1, page 1, line 22). The "*Effects of BR3-Fc Polypeptides in* in vivo *lupus model*" are tested in Example 7 (see pages 130 and 131). Figures 11A to 11D show that the treatment resulted in reduced proteinurea levels (a symptom of lupus), enhanced survival and fewer anti-dsDNA antibodies than in control-treated mice. The last sentence on page 131 summarises that "[t]*hese data suggest that BR3-Fc treatment blocked production of auto-antibodies by B cells in the lupus mice and enhanced survival by blocking TALL-1 function* in vivo." This confirms the proposed solution in document E18, i.e. that blocking the BLyS (TALL-1) system was effective in treating autoimmune diseases.

15. The respondent argued that the skilled person seeking a solution to the objective technical problem, would

dismiss the disclosure in document E1 in view of the teaching in documents E8 and E9, which taught away from the solution proposed in document E18. Document E8 raised questions as to the relevance of anti-DNA antibodies (see page 827, left-hand column, second-to-last paragraph: "*In SLE, anti-DNA antibodies are not related closely to clinical improvement, but the pathogenicity of these antibodies is uncertain.*") and plasma cells (see page 827, right-hand column, second paragraph: "*our understanding of human B-lymphocyte and plasma cell kinetics is rudimentary*"). Document E9 disclosed that the "*role of BAFF* [BLyS] *in the generation and survival of memory cells is also currently unexplored*", that "*BAFF* [BLyS] *dependence* [of plasma cells] *needs to be established*" (see document E9, page 242, second paragraph) and that "several observations *call into question the involvement of BAFF [BLyS] in the GC reaction*" (see page 244, second paragraph).

16. The board does not agree. Document E8 also states that "*longer-term remission in autoimmune disease may only be achievable if B-lymphocyte depletion is combined with some form of plasma cell depletion strategy*". It then concludes that "[a]*t present, no safe and effective anti-plasma cell agents are available, but increased understanding of the survival signals required by plasma cells may lead to new therapeutic avenues*" (page 828, left-hand column, last paragraph). The skilled person thus learned from document E8 that targeting the survival signals required by plasma cells as proposed in document E18 and exemplified in document E1 was an avenue worth pursuing.

17. Document E9 is a scientific review article which identifies certain knowledge gaps about BLyS (BAFF).

The board notes, however, that document E9 concludes on a rather confident note by stating that "[t]*he biochemical and genetic dissection of the BAFF* [BLyS] *system has yielded a clear and relatively unambiguous picture of an obligate survival signal for both maturing and fully differentiated B cells*" (page 253, last paragraph). The board is hence satisfied that document E9 teaches that BLyS is required for B cells to survive, which is in line with the teaching of documents E18 and E1.

18. The board further notes that document E1 was published after documents E8 and E9, meaning that the skilled person would consider document E1 to independently disclose information of which the authors of documents E8 and E9 might not have been aware when drafting the review articles. The board therefore sees no merit in the argument that the skilled person would dismiss combining the disclosure of document E18 with the teaching in document E1.

19. The respondent further argued that the suggested interference "*with these potent survival signals directed toward membrane-associated receptors on peripheral B cells*" (in this case by using agents which block the BLyS/BAFF/zTNF4 system) in document E18 (page 1490, right-hand column, second paragraph) was only one alternative available to the skilled person for improving the efficacy of rituximab treatment, and that choosing this particular alternative was not obvious to the skilled person.

20. The board does not agree, because all the listed alternatives are disclosed as being equally valid (see document E18, page 1490, right-hand column, second paragraph: "*...addition of second agents, such as*

conventional chemotherapeutic drugs. Alternatively, it is likely that future studies will also evaluate co-treatments with specific biologic agents to interfere with T cell helper signals, such as ... As an alternative approach it may be desirable to utilize agents that block the recently discovered BLyS/BAFF/ zTNF4 system") and there was no reason for the skilled person to reject any one of them. Selecting one of the suggested alternatives for improving the efficacy of rituximab, and thus one of several obvious courses of action, cannot involve an inventive step.

21. The question remains whether the skilled person, having regard to the combined teachings of documents E18 and E1, would reasonably have expected an improved therapy as a result of improved depletion of B cells by combining rituximab with a BLyS antagonist (e.g. BR3-Fc) and not just the same level of depletion as with rituximab alone.

22. In Figure 2, document E18 discloses cells which do not express CD20 ("CD20-neg"; see figure legend: "*CD20 is expressed only at intermediate stages and not on plasma cells*"). On page 1489, right-hand column, last paragraph, the authors find it "*likely that the dominant cellular source of disease-associated autoantibodies, especially IgG antibodies, are plasma cells that do not bear CD20 (Figure 2)*" and that "*plasma cells may still continue to produce disease-causing autoantibodies*". Since document E18 goes on to state that "*optimal treatment of diseases that have autoantibody-mediated pathology may require a regimen that also affects plasma cells*", the board concludes that the suggestion in document E18 to use an "*agent that blocks BLyS/BAFF/zTNF4*" (page 1490, right-hand column, second paragraph) in combination with the CD20-

binding antibody rituximab was aimed at addressing non-CD20 cells, e.g. plasma cells, "*the major source of antibodies in the body*" (see sentence bridging pages 1485 and 1486). Furthermore, Example 7 of document E1 demonstrates that anti-DNA autoantibodies and proteinurea - a hallmark of SLE - are reduced after BR3-Fc administration, thus confirming that "*BR3-Fc treatment blocked production of auto-antibodies by B cells in the lupus mice and enhanced survival by blocking TALL-1 function in vivo*" (see last sentence on page 131).

23. In view of the above-mentioned disclosures, the board concludes that the skilled person was aware that targeting BLyS with a soluble BR3-Fc immunoadhesin could result in the depletion of autoantibody-producing cells lacking CD20, including plasma cells (see also points 13. and 14. above).

24. The skilled person therefore had a reasonable expectation that the combined use of a CD20-binding antibody and a BLyS antagonist (such as a BR3-Fc immunoadhesin) would result in the depletion of additional (non-CD20) B cell types, such as plasma cells. It was therefore obvious to the skilled person to combine rituximab with a BLyS antagonist for an improved method for alleviating B cell regulated autoimmune disorders.

25. In view of the above considerations, the claimed subject-matter does not involve an inventive step.

Auxiliary request 2

Inventive step (Article 56 EPC) - claim 1

26. The claimed subject-matter differs from that of claim 1 of the main request in that it is specified that "the BLyS antagonist is an anti-BLyS antibody". The respondent has not argued that this feature alters the technical effect resulting from the difference between the claimed subject-matter and the rituximab therapy disclosed in document E18. In the context of sufficiency of disclosure, the respondent has further argued that "*there is a clear expectation from the patent disclosure that an anti-BLyS antibody that blocks BR3 interaction with a BLyS polypeptide can be used to provide the same antagonist effect* [as a BR3 immunoadhesin]" (see reply to the statement of grounds of appeal, page 14). The objective technical problem is therefore not different from that outlined above for the main request and auxiliary request 1 (see point 8. above).

27. The question which has to be answered is thus whether the skilled person, when starting from the rituximab therapy disclosed in document E18 representing the closest prior art and further consulting document E1, would have used an anti-BLyS antibody to block the BLyS system. Document E1 discloses that "*TALL-1* [BLyS] *antagonists and APRIL antagonists contemplated for use further include anti-TALL-1* [BLyS] *antibodies... capable of blocking or reducing binding of the respective ligand to the TACIs or BR3 receptors*" (see page 11, lines 5 to 8). In the opinion of the board, the skilled person would therefore have considered an anti-BLyS antibody as an obvious alternative to the BR3-Fc immunoadhesin tested in Example 7 of document

E1. It would further have been evident to the skilled person in view of the teaching in document E1 that the interaction between BLyS and BR3 could be blocked in both directions, i.e. by "a*nti-TALL-1* [BLyS] *antibodies ... capable of blocking or reducing binding of the respective ligand* [BLyS]" or by "*an antagonist (such as a BR3 immunoadhesin) which blocks or neutralizes activity of TALL-1* [BLyS]" (see page 11, lines 7 to 8 and lines 19 to 20).

28. The skilled person would therefore have considered combining a CD20-binding antibody with an anti-BLyS antibody capable of blocking or reducing binding of the respective ligand to the TACIs or BR3 receptors to alleviate B cell regulated autoimmune disorders as one of several obvious solutions available to improve the prior-art method. The claimed subject-matter thus lacks an inventive step.

Auxiliary request 3

Admittance (Article 12(4) RPBA 2007)

29. The appellant challenged the admittance of auxiliary request 3 into the appeal proceedings. The board decided to consider the request but in view of the negative decision on inventive step (see below) sees no need to provide reasons for this decision.

Inventive step (Article 56 EPC)

30. The subject-matter of claim 1 differs from that of claim 1 of the main request in that "the BLyS antagonist is an anti-BLyS antibody and wherein the anti-BLyS antibody partially or fully blocks BR3

interaction with a BLyS polypeptide". As no further effect is linked to this additional feature, the objective technical problem is identical to that outlined above for the main request (see point 8. above).

31. According to page 15, lines 19 to 21 of document E1, "[t]*he terms 'BR3', 'BR3 polypeptide' or 'BR3 receptor' when used herein encompass 'native sequence BR3 polypeptides'*". Also, in view of the disclosure on page 11, lines 5 to 8 (see point 27. above), document E1 thus teaches that the disclosed anti-BLyS antibodies are capable of blocking the binding of BLyS to BR3.

32. The claimed subject-matter therefore lacks an inventive step for the same reasons as set out in point 28.

Auxiliary requests 4 and 5

Inventive step (Article 56 EPC)

33. Claim 1 of auxiliary request 4 is identical to claim 1 of auxiliary request 2, and claim 1 of auxiliary request 5 is identical to claim 1 of auxiliary request 3 (see section IV).

34. The subject-matter of these claims thus lacks an inventive step for the same reasons as outlined above for auxiliary requests 2 and 3 (see points 26. to 32. above).

Auxiliary requests 6 to 11

Inventive step (Article 56 EPC) - claim 1

35. The respondent has not further argued to the effect that the claimed subject-matter of these requests involves an inventive step, in particular in view of a combination of the disclosures in documents E18 and E1. Moreover, the board notes that the specific disease systemic lupus erythematosus (SLE) now referred to in the claim is also disclosed in document E1 (Example 7 and claims). The addition of this feature hence fails to result in subject-matter involving an inventive step.

36. Thus this claimed subject-matter equally lacks an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

A. Chavinier Tomsic B. Claes

Decision electronically authenticated