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Datasheet for the decision of 4 July 2023

Case Number: T 2347/19 - 3.3.07

Application Number: 11788077.3

Publication Number: 2637670

IPC: A61K31/573, A61K39/395

Language of the proceedings: EN

Title of invention:
PREVENTION OF ADVERSE EFFECTS CAUSED BY CD3 SPECIFIC BINDING DOMAINS

Patent Proprietor:
Amgen Research (Munich) GmbH

Opponents:
F.Hoffmann-La Roche AG
Lindis Biotech GmbH

Headword:
Blinatumomab neurological adverse events/AMGEN

Relevant legal provisions:
EPC Art. 83, 56
RPBA Art. 12(4)

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It can be changed at any time and without notice

Keyword:
Sufficiency of disclosure - after amendment
Inventive step - after amendment

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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 2347/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 4 July 2023

Appellant: (Patent Proprietor)	Amgen Research (Munich) GmbH Staffelseestrasse 2 81477 München (DE)
Representative:	Schiweck Weinzierl Koch Patentanwälte Partnerschaft mbB Ganghoferstraße 68 B 80339 München (DE)
Appellant: (Opponent 1)	F.Hoffmann-La Roche AG 124 Grenzacherstrasse 4070 Basel (CH)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Party as of right: (Opponent 2)	Lindis Biotech GmbH Am Klopferspitz 19 82152 Martinsried (DE)
Representative:	Graf von Stosch, Andreas Graf von Stosch Patentanwaltsgesellschaft mbH Prinzregentenstraße 22 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 June 2019 concerning maintenance of the European Patent No. 2637670 in amended form**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	L. Bühler

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's interlocutory decision rejecting the main request and finding that European patent No. 2 637 670 as amended according to auxiliary request 1, and the invention to which it relates, met the requirements of the EPC.

Claim 1 of the main request read as follows:

"*1. Glucocorticoid (GC) for use in a method of prophylaxis of neurological adverse events caused by the administration of a CD3 binding domain, wherein the GC is administered prior to the administration of the first dose of the CD3 binding domain and prior to the administration of the second dose and/or third dose of the CD3 binding domain, wherein a first dose of the CD3 binding domain is administered for a first period of time and consecutively a second dose of the CD3 binding domain is administered for a second period of time, wherein the second dose exceeds the first dose, wherein the GC is dexamethasone, wherein said neurological adverse event is one or more of disturbances of the senses, seizures, encephalopathy, cerebral edema, confusion, ataxia, apraxia, speech disorder, paresis, tremor, or disorientation.*"

Claim 1 of the request held allowable by the opposition division differed from claim 1 of the main request in that the CD3 binding domain was specified to be a CD19xCD3 bispecific single chain antibody.

II. The documents cited by the parties in these opposition and appeal proceedings included the following:

D2 WO 2007/068354

D3 M. Goebeler et al., 15th Congress of the European Hematology Association, Barcelona, 10-13 June 2010, Abstract No. 0559

D5 WO 2012/055961

D6 US 61/407107 (priority application of D5)

D8 WO 2011/051307

D9 L. Chatenoud et al., Transplantation, 51(2), 1991, 334-8

D10 R. Peces et al., Nephron, 63, 1993, 118

D11 T.D. Rozen, Current Treatment Options in Neurology, 4, 2002, 395-401

D12 M. Guarino et al., European Journal of Neurology, 13, 2006, 2-9

D14 S. Breslin, Clinical Journal of Oncology Nursing, supplement to vol. 11(1), 2007, 37-42

D15 C. Brandl et al., Cancer Immunol Immunother, 56, 2007, 1551-63

D16 B. Schlereth et al., Cancer Immunol Immunother, 55, 2006, 503-14

D17 A. Shih et al., Journal of Pain & Palliative Care Pharmacotherapy, 21(4), 2007, 69-76

D18 J.E. Benjamin et al., Ther Adv Hematol, 7(3), 2016, 142-56

D19 K.J. Lee et al., Therapeutics and Clinical Risk Management, 12, 2016, 1301-10

D20 WO 2006/114115

D21 PhD dissertation of Matthias Klinger, Eberhard Karl University, Tübingen, 2009

D22 H. Inaba et al., Lancet Oncol, 11(11), 2010, 1096-106

D30 US 61/412229 (priority application of the patent in suit)

D31 WO 2008/119567

D34 R. Bargou et al., Science, 321, 2008, 974-7

D34a Supporting online material for D34

D39 FDA CDER, Blinatumomab/Blincyto Medical Review, 2014

D41a P.H. Went et al., Human Pathology, 35(1), 2004, 122-8

D41b D. Walsh et al., Cleveland Clinic Journal of Medicine, 59, 1992, 505-15

D42 L.H. Sehn et al., Hematological Oncology, 37(52), 2019

III. In the decision under appeal, the opposition division held that the subject-matter of claim 1 of the main request was not sufficiently disclosed because it had not been made credible that the claimed prophylactic effect could be achieved when the CD3 binding domain was not a CD19xCD3 bispecific single chain antibody or when the disease treated was not lymphoma or leukaemia.

With regard to auxiliary request 1, the opposition division concluded, *inter alia*, that:

- the limitation of the CD3 binding domain in claim 1 to a C19xCD3 bispecific single chain antibody overcame the sufficiency objection
- the relevant subject-matter in D5 did not belong to the prior art because it had the same effective date as the patent
- the closest prior art was D8 rather than D2
- the subject-matter of claim 1 was a non-obvious solution to the objective technical problem of providing an alternative method for reducing central nervous system side effects in lymphoma patients treated with a CD19xCD3 bispecific single chain antibody

IV. The patent proprietor (appellant-patent proprietor) and opponent 1 (appellant-opponent) each filed an appeal against the decision.

Opponent 2 (party as of right) did not file any appeal.

V. With its statement of grounds of appeal, the appellant-patent proprietor filed nine sets of claims as its main request and auxiliary requests 1 to 8. It also filed documents D41a and D42.

The main request is identical to the main request on which the decision under appeal is based.

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the CD3 binding domain is specified to be a bispecific antibody.

Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it specifies that the neurological adverse events are caused in a leukaemia or lymphoma patient.

Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that the CD3 binding domain is specified to be a CD19xCD3 bispecific antibody.

Auxiliary requests 4 is identical to the request held allowable by the opposition division. It reads as follows:

"*1. Glucocorticoid (GC) for use in a method of prophylaxis of neurological adverse events caused by the administration of a CD3 binding domain, wherein the GC is administered prior to the administration of the*

first dose of the CD3 binding domain and prior to the administration of the second dose and/or third dose of the CD3 binding domain, wherein a first dose of the CD3 binding domain is administered for a first period of time and consecutively a second dose of the CD3 binding domain is administered for a second period of time, wherein the second dose exceeds the first dose, wherein the GC is dexamethasone, wherein said neurological adverse event is one or more of disturbances of the senses, seizures, encephalopathy, cerebral edema, confusion, ataxia, apraxia, speech disorder, paresis, tremor, or disorientation, wherein said CD3 binding domain is a CD19xCD3 bispecific single chain antibody."

VI. With its statement of grounds of appeal, the appellant-opponent filed, *inter alia*, documents D34a and D41b and a new inventive-step objection based on documents D34/D34a as the closest prior art.

VII. Each appellant replied to the statement of grounds of appeal of the other appellant.

VIII. The board scheduled oral proceedings, in line with the appellants' requests, and issued a communication including its preliminary opinion on the case.

IX. Oral proceedings were held by videoconference, as agreed by the appellants. The party as of right was absent, as previously announced.

At the end of the oral proceedings, the board announced its decision.

X. The appellant-patent proprietor's arguments relevant to the present decision can be summarised as follows.

Main request - sufficiency of disclosure

The examples in the patent demonstrated the prophylactic effect of dexamethasone on the neurological adverse events (NAEs) caused by the CD19xCD3 single chain antibody blinatumomab in leukaemia and lymphoma patients. No serious doubts had been raised that this effect could be generalised to the prevention of NAEs caused by any CD3 binding domain in any patient.

Documents D3, D8 to D12, D14 to D16, D18, D19, D21, D31 and D42 demonstrated the common general knowledge that CD3 binding domains generally cause the NAEs recited in claim 1. The fact that CD19 binding domains or certain disorders could also cause NAEs did not render the claimed subject-matter insufficiently disclosed. The patent (paragraph [0025]) taught how to find out whether the cause of the NAEs was the CD3 binding domain.

Auxiliary requests 1 to 3 - admittance

The filing of auxiliary requests 1 to 3 was a direct reaction to the decision under appeal. At the oral proceedings, the opposition division changed its position compared to its preliminary opinion in preparation for the oral proceedings, taking the appellant-patent proprietor by surprise. The reasons given by the opposition division for considering the subject-matter of the main request insufficiently

disclosed were not those considered relevant in the preliminary opinion.

Auxiliary request 4 - sufficiency of disclosure

The limitation of the CD3 binding domain in claim 1 of auxiliary request 4 to a CD19xCD4 bispecific single chain antibody aligned the claimed subject-matter with the examples in the patent. This limitation implied a specific mode of action and the treatment of blood cancer. The examples in the patent made credible that dexamethasone prevented the occurrence of blinatumomab NAEs when the two compounds were administered according to the regimen of claim 1. The appellant-opponent had not raised serious doubts against this evidence. It was not necessary to incorporate the dosing schedule of the examples in claim 1. The patent provided sufficient orientation in this respect.

Auxiliary request 4 - novelty

Paragraph [0141] of D5 could not anticipate the subject-matter of claim 1 of auxiliary request 4 because it did not belong to the prior art. The teaching of paragraph [0141] was not disclosed in D6, the priority application of D5.

The passages cited by the appellant-opponent on pages 22, 37 and 38 of D6 did not disclose the administration of dexamethasone prior to the first dose and prior to the second and/or the third dose of the CD19xCD3 bispecific single chain antibody.

Auxiliary request 4 - priority

The feature in claim 1 that dexamethasone was administered prior to the first dose and prior to the second and/or the third dose of the antibody was clearly and unambiguously derivable from a reading of the priority application (D30) in its entirety, e.g. from the examples on pages 17 to 19, page 6, lines 10 to 21, page 15, lines 8 to 11, page 16, lines 6 to 9, page 18, line 29 to page 19, line 14, and claims 1 and 2. Therefore, the priority date of 10 November 2020 was validly claimed, and D8 could not be cited against inventive step.

Auxiliary request 4 - inventive step starting from D2

D2 (page 2, second paragraph) dealt with the prevention of adverse events occurring immediately after infusion of a CD19xCD3 bispecific single chain antibody. These adverse events were associated with a massive release of cytokines. Their symptoms included hypotension, pyrexia, fatigue, vomiting, tachycardia, hypertension, headache and back pain.

The subject-matter of claim 1 differed from the treatment in Example 5 of D2 not only in the glucocorticoid and the administration of the glucocorticoid before the second and/or the third dose of the antibody. It also differed in the nature of the prevented adverse events. Contrary to the adverse events of D2, the NAEs of claim 1 were not necessarily associated with the cytokine release syndrome (D31, page 976, middle column). They did not necessarily occur immediately after infusion but could also occur days later (patent, reference examples in paragraphs

[0075] to [0082] and D39, page 5, second paragraph and pages 56 and 57, Figures 2 and 3). These differences produced the technical effect of preventing the NAEs caused by the administration of the C19xCD3 bispecific single chain antibody, including those not related to the cytokine release syndrome and which occurred at later stages of the treatment. This effect was demonstrated in the patent (paragraphs [0083] to [0092]).

Consequently, the objective technical problem was the prevention of further adverse events caused by the administration of a CD19xCD3 bispecific single chain antibody, especially those occurring at late stages of the treatment.

The solution proposed in claim 1 was not obvious because D2 was silent on NAEs, especially those produced at later stages of antibody administration. It could not be concluded from Example 5 of D2 that NAEs were prevented since NAEs did not occur in every patient and the example involved the treatment of only two patients. The skilled person had no motivation to add the glucocorticoid prior to the second and/or the third dose since D2 did not teach that NAEs could occur later in the treatment. Neither did D17 and D22 motivate the skilled person to use dexamethasone instead of methylprednisolone since the two glucocorticoids had different properties and no success could be expected.

Auxiliary request 4 - inventive step starting from D8

Like the patent, D8 was directed to the reduction of NAEs arising upon administration of a CD19xCD3 bispecific single chain antibody. According to D8 (page

5, lines 22 to 27 and Examples 6 and 7), patients having a B:T cell ratio of 1:5 or lower had a higher risk of suffering NAEs. Those high risk patients could be successfully treated with a two-step dosage regimen starting from a lower dose administered for one week followed by a higher dose administered for the rest of the treatment. The prophylactic measures of D8 did not include the administration of a glucocorticoid. Dexamethasone was used but for treating NAEs that had already occurred. Therefore, the difference of the subject-matter of claim 1 over D8 was the prophylactic use of dexamethasone prior to the first and prior to the second and/or the third dose of the antibody.

This difference resulted in a reliable, standardised prophylaxis of severe NAEs. D8 (Example 7) and the patent (paragraphs [0072] to [0082]) showed that, even when the dosage regimen of D8 was used, patients suffered NAEs that led to treatment interruption. In contrast, the administration of dexamethasone prophylaxis according to claim 1 prevented the occurrence of NAEs that would have led to treatment interruption. Therefore, the objective technical problem solved by the subject-matter of claim 1 was the provision of a reliable, standardised prophylaxis for safely administering a C19xCD3 bispecific single chain antibody to a patient without discontinuation of the therapy due to severe NAEs.

The solution of claim 1 was not obvious from D8, which did not suggest the prophylactic administration of dexamethasone. Neither was the solution obvious from the combination of D8 with D34/D34a or D20. D34/D34a and D20 did not deal with the prevention of NAEs but with the reduction of side effects produced by cytokine release. In addition, D34/D34a and D20 did not disclose

the administration of dexamethasone prior to the first dose of the antibody and prior to the second and/or the third dose. The prophylactic use of dexamethasone in Example 5 of D20 was not aimed at reducing NAEs.

XI. The appellant-opponent's arguments relevant to the present decision can be summarised as follows.

Main request - sufficiency of disclosure

The method of claim 1 was not reproducible across the whole breadth of the claim. The examples in the patent were directed to the prophylactic effect of dexamethasone against NAEs caused by blinatumomab in the treatment of leukaemia or lymphoma patients. Blinatumomab was a C19xCD3 bispecific single chain antibody that bound concomitantly to T-cells and B-cells. It activated T-cells to kill malignant B-cells in leukaemia or lymphoma patients. In contrast, CD3 binding domains were a vast number of possible molecules with a full range of functions, modes of action and potential adverse effects. For instance, the CD3 binding antibody OKT3 exhibited two opposed effects: activating and blocking T-cells (D31, page 2, second paragraph), and was generally used as an immunosuppressive agent. Therefore, it was neither credible that CD3 binding domains generally caused NAEs nor that the NAEs caused by any CD3 binding domain could be prevented with dexamethasone.

Auxiliary requests 1 to 3 - admittance

Auxiliary requests 1 to 3 should not be admitted because they could have been filed in the opposition proceedings. The opposition division changing its mind during the oral proceedings to agree with arguments

provided by the opponents was not surprising but a possible development in the proceedings. Moreover, at the oral proceedings, the appellant-patent proprietor had time to react to the opposition division's change of mind.

Auxiliary request 4 - sufficiency of disclosure

Claim 1 lacked features essential for carrying out the invention. On the one hand, the claim did not specify the part of the CD3 receptor bound by the CD19xCD3 bispecific single chain antibody, namely the epsilon chain. Binding a different part of the receptor would result in a different effect on the T-cell (D31, page 2, lines 5 to 10 and page 3, lines 12 to 23). On the other hand, documents D2 (page 18, second paragraph and Example 5) and D8 (page 12, second paragraph) showed that a reduction of the occurrence of adverse events was due to the mode of administration and the dosing regimen of blinatumomab rather than to the action of dexamethasone. Therefore, the dosage regimen of the examples had to be incorporated into claim 1. Moreover, the prophylactic effect of dexamethasone had not been made credible, let alone for each of the NAEs recited in claim 1.

Auxiliary request 4 - novelty

The disclosure in paragraph [0141] of D5 belonged to the prior art and anticipated the subject-matter of claim 1. The teaching of paragraph [0141] was disclosed in D6, the priority application of D5.

According to D6, page 22, lines 22 to 34, dexamethasone was co-administered for preventing NAEs, one of the options being pre-administration. The administration of

dexamethasone prior to the second and/or the third dose of the antibody was derivable from D6, page 37, line 30 to page 38, line 2 and page 38, lines 13 to 21.

Auxiliary request 4 - priority

The priority application D30, in particular the examples on pages 17 to 19, did not disclose the use of dexamethasone prior to the first and prior to the second and/or the third doses of the antibody. Therefore, claim 1 of auxiliary request 4 did not enjoy the priority date of 10 November 2010, and D8 belonged to the prior art citable for inventive step.

Auxiliary request 4 - inventive step starting from D2

Like the patent, D2 was concerned with the prevention of infusion-related adverse events produced by the administration of a C19xCD3 bispecific single chain antibody. According to D2 (page 18, second paragraph and page 2, second paragraph), bolus administration of the antibody produced a burst-like activation of T-cells and their migration to the tissues. This produced adverse events such as, but not only, the cytokine release syndrome. The same explanation had been put forward by the appellant-patent proprietor in its statement of grounds of appeal (paragraph 53) for the occurrence of NAEs. The appellant-patent proprietor had referred to D31 (passage bridging pages 7 and 8). With regard to the time of occurrence, NAEs also happened at the beginning of infusion concurrent with the cytokine release syndrome (D39, pages 56 and 57, Figures 2 and 3). Therefore, the NAEs in claim 1 of auxiliary request 4 were not different from the adverse events dealt with in D2; they were associated with the cytokine release induced upon infusion of the antibody.

D2 (page 21, second paragraph and claim 1) taught that the tolerability of the antibody could be improved by decreasing the dose given per time unit and prolonging patient exposure to the antibody. This measure was illustrated in Example 5 of D2, in which the glucocorticoid methylprednisolone was additionally administered to suppress the cytokine release induced by antibody infusion. The treatment of Example 5 was carried out for two and four weeks, and no significant adverse events, including NAEs, were reported.

The subject-matter of claim 1 differed from D2 in the nature of the glucocorticoid and in that it was administered not only before the first dose of the antibody but also before the second and/or the third doses. The examples in the patent did not demonstrate any technical effect associated with these differences.

Therefore, the objective technical problem was the provision of alternative means for improving the tolerability of the administration of a CD19xCD3 bispecific single chain antibody.

The solution proposed in claim 1 was obvious. The skilled person knew from D17 and D22 that methylprednisolone could be exchanged with dexamethasone. Furthermore, the addition of the glucocorticoid before the second and/or the third dose of the antibody was arbitrary and had no associated technical effect.

Auxiliary request 4 - inventive step starting from D8

According to D8 (page 38, lines 14 to 16), the administration of a CD19xCD3 bispecific single chain antibody produced NAEs only in a subset of patients. D8

disclosed how to assess whether patients belonged to that subset and disclosed a dosage regimen for them. The subject-matter of claim 1 differed from the dosage regimen of D8 in that dexamethasone was administered prophylactically prior to the first dose and prior to the second and/or the third dose of the antibody. This difference had the technical effect of reducing the occurrence of NAEs. The objective technical problem was the provision of an alternative method for reducing NAEs in CD19xCD3 bispecific single chain antibody treatment of lymphoma patients.

The solution proposed in claim 1 was obvious in light of documents D34/D34a or D20, which dealt with the reduction of infusion-related side effects arising from antibody therapy. The documents suggested the prophylactic administration of a glucocorticoid before starting the treatment with the antibody. In Example 5 of D20, the glucocorticoid was dexamethasone.

XII. The party as of right did not make any substantive submissions or requests in these appeal proceedings

XIII. The appellants' final requests relevant to this decision were as follows.

The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request or, alternatively, one of auxiliary requests 1 to 8, all filed with the statement of grounds of appeal. The appellant-patent proprietor also requested that documents D41a and D42 be admitted into the appeal proceedings and that documents D34a and D41b not be admitted.

The appellant-opponent requested that the opposition division's decision be set aside and that the patent be revoked in its entirety. It also requested that auxiliary requests 1 to 3 not be admitted into the proceedings and that document D34a be admitted.

Reasons for the Decision

1. Main request - sufficiency of disclosure (Article 83 EPC)

1.1 Claim 1 of the main request is directed to the use of dexamethasone for preventing NAEs caused by the administration of a CD3 binding domain. This use was illustrated in the examples of the application as filed for the CD3 binding domain blinatumomab, a CD19xCD3 bispecific single chain antibody.

The parties disputed whether the teaching on blinatumomab in the examples of the application as filed could be generalised to any CD3 binding domain.

The appellant-patent proprietor submitted (statement of grounds of appeal, paragraphs 47 and 49) that, at the priority date, it was common general knowledge that CD3 binding domains generally cause NAEs, in particular the NAEs recited in claim 1 of the main request. Therefore, the NAEs prevented by dexamethasone in the examples of the application as filed could be explained by the fact that blinatumomab was a CD3 binding domain. It was credible that dexamethasone would also prevent the NAEs caused by any other CD3 binding domain.

1.2 The board disagrees. According to the application as filed (paragraphs [0006] to [0010] and the examples), blinatumomab was undergoing clinical trials which had revealed that it caused NAEs. The application neither disclosed the mechanism underlying the observed NAEs nor provided evidence allowing the conclusion that the NAEs were univocally caused by the binding of the CD3 receptor on T-cells. The mechanism by which dexamethasone prevented the NAEs caused by blinatumomab was not disclosed either.

The term "CD3 binding domain" encompasses a vast range of substances, including, *inter alia*, small peptides, antibody constructs and engineered proteins. These substances may exert different biological functions, even with opposite effects. For instance, the CD3-specific antibody OKT3 may both activate or block T-cells in a time-dependent fashion (D31, page 2, second paragraph). As the mechanisms by which blinatumomab causes NAEs and dexamethasone prevents those NAEs were unknown at the filing date and the NAEs could not be univocally attributed to the fact that blinatumomab binds the CD3 receptor, there was no scientific rationale for the skilled person to conclude that dexamethasone could prevent the NAEs caused by any CD3 binding domain within any therapeutic context.

1.3 Therefore, the subject-matter of claim 1 of the main request is not sufficiently disclosed.

2. Auxiliary requests 1 to 3 - admittance (Article 12(4) RPBA 2007)

2.1 The appellant-patent proprietor filed auxiliary requests 1 to 3 with its statement of grounds of appeal as new intermediate fall-back positions between the

main request and the request held allowable by the opposition division, now auxiliary request 4.

2.2 The patent proprietor (statement of grounds, pages 9 to 12; reply to the appeal, pages 6 and 7) justified the filing of the new auxiliary requests as a reaction to the arguments against sufficiency of disclosure of the main request in the decision under appeal. The opposition division had indicated in its preliminary opinion that the main issue for sufficiency of disclosure was whether the discontinuation of the treatment in the patent examples in which patients had not been pre-treated with dexamethasone was due to the occurrence of NAEs. Other objections raised by the opponents had not been considered persuasive by the opposition division. However, during the oral proceedings, the opposition division concluded that the subject-matter of the main request was not sufficiently disclosed because the effect shown in the patent for a CD19xCD3 bispecific single chain antibody could not be generalised to any CD3 binding domain.

2.3 The board agrees with the appellant-opponent that the appellant-patent proprietor could and should have filed auxiliary requests 1 to 3 in the opposition proceedings.

2.3.1 In its preliminary opinion (page 8, lines 7 and 8), the opposition division did not agree with the opponents that the lack of a causative link between binding the CD3 receptor and the occurrence of NAEs was problematic. At the oral proceedings before the opposition division (minutes, page 2), the parties discussed sufficiency of disclosure in relation to the generalisation of the effect shown in the application as filed for a CD19xCD3 antibody construct. In the

decision (point 19.4), the opposition division adopted the opponents' argument that the subject-matter of the main request was not sufficiently disclosed because the effect shown for a CD19xCD3 bispecific single chain antibody could not be extended to any CD3 binding domain.

2.3.2 A preliminary opinion in preparation for the oral proceedings is not binding and may change during the oral proceedings. A change of mind of the opposition division following discussion at the oral proceedings to take up arguments considered not convincing in its preliminary opinion is a possible development in the proceedings and cannot come as a surprise.

Furthermore, it is apparent from the minutes of the oral proceedings on 17 April 2019 (page 2, penultimate sentence) that, after the rejection of the main request, the appellant-patent proprietor had time during the lunch break to reflect on how to proceed. At that time, the patent proprietor did not make any attempt to overcome the sufficiency objection by filing a new claim request. It instead stated that it wanted to proceed with the then pending auxiliary request 1.

2.4 At the oral proceedings before the board, the appellant-patent proprietor did not submit any argument on this point. Therefore, auxiliary requests 1 to 3 were not admitted into the appeal proceedings pursuant to Article 12(4) RPBA 2007.

3. Auxiliary request 4 – sufficiency of disclosure (Article 83 EPC)

3.1 The appellant-opponent submitted that the subject-matter of claim 1 of auxiliary request 4 was not sufficiently disclosed for three reasons:

- claim 1 did not indicate the part of the CD3 receptor bound by the antibody
- claim 1 did not indicate the mode of administration and the dosing regimen of the antibody, features essential for achieving a reduction of the NAEs
- the prophylactic effect of dexamethasone had not been demonstrated, let alone for each of the NAEs recited in claim 1

3.2 The board is not convinced by these arguments. Even though the CD3 binding domain in claim 1 is not limited to blinatumomab, the limitation to a CD19xCD3 bispecific single chain antibody and the administration schedule defined in claim 1 are closely aligned with the teaching that can be drawn from the examples in the application as filed.

3.2.1 It is apparent that a CD19xCD3 bispecific single chain antibody implies a mode of action and a therapeutic indication: the antibody is conceived for concomitantly binding the CD3 receptor of a T-cell and the CD19 receptor of a B-cell; this double binding activates a T-cell to kill a malignant B-cell in blood cancer therapy. Blinatumomab was the prominent representative of CD19xCD3 bispecific single chain antibodies at the filing date. The application as filed showed that the continuous intravenous administration of blinatumomab to lymphoma patients at escalating doses produces NAEs

(paragraphs [0080] to [0085]) and that these NAEs may be prevented or reduced by the prophylactic administration of dexamethasone (paragraphs [0087, second part] and [0094]). Considering that CD19xCD3 bispecific single chain antibodies are intended to treat the same conditions and by the same mode of action as blinatumomab, no serious doubts arise that dexamethasone will also be suitable for preventing or reducing the NAEs occurring by the administration of CD19xCD3 bispecific single chain antibodies other than blinatumomab. Therefore, contrary to the appellant-opponent's view, claim 1 does not need to specify the part of the CD3 receptor bound by the antibody.

3.2.2 Claim 1 defines an administration schedule for both the CD19xCD3 bispecific single chain antibody and dexamethasone. A first dose of the antibody is administered for a first period of time, and a second dose, which exceeds the first dose, is administered for a second period of time. Dexamethasone is administered prior to the first dose of the antibody and prior to the second dose and/or the third dose of the antibody.

The application as filed shows in paragraphs [0080] to [0085] that blood cancer patients treated with blinatumomab dose escalation steps may develop NAEs several days after starting the therapy. These reference examples reflect the administration schedule proposed in D2 and D8 and, contrary to the appellant-opponent's contention, it could not prevent blinatumomab NAEs in blood cancer therapy: the patients experienced apraxia, tremor, speech disturbances and paresis. When NAEs occurred, they were treated with dexamethasone. However, in the cases in paragraphs [0081] and [0085], the curative administration of

dexamethasone could not reduce the NAEs sufficiently, and the patients had to interrupt the cancer therapy.

In contrast, the patients in paragraphs [0086] to [0090] of the application as filed were treated according to the administration schedule of claim 1 and did not have to discontinue the therapy due to NAEs. Blinatumomab was administered at dose escalation steps with dexamethasone prophylaxis before the start of the treatment and before each dose escalation step. The treatments included a group of five patients disclosed in the second part of paragraph [0087] and a cohort of five patients treated with the so-called early dexamethasone schedule in paragraph [0094].

The board notes that the application does not specify whether the patients in paragraphs [0086] to [0090] experienced NAEs but only that they did not need to stop the treatment due to NAEs. The board is also aware that the number of patients treated in those tests is low and that, as indicated in the application as filed (paragraph [0007], last sentence) and in D8 (page 3, lines 9 to 13 and page 38, lines 14 to 16), the percentage of patients receiving blinatumomab who generally experience NAEs is in the order of 20 to 30%. However, in spite of the limited conclusions that may be drawn from the examples in paragraphs [0086] to [0090] of the application as filed, the board considers that the examples make it more likely than not that dexamethasone, administered as defined in claim 1, indeed prevents the occurrence, or at least the severity, of the NAEs that arise when blinatumomab is administered in dose escalation steps.

3.2.3 With regard to the alleged need to specify the doses of the antibody and dexamethasone in the claim (appellant-

opponent's statement of grounds of appeal, page 32, last paragraph), the board agrees with the appellant-patent proprietor (reply to the appellant-opponent's appeal, sentence bridging pages 26 and 27) that the application as filed provides sufficient orientation in paragraphs [0032], [0033], [0035], [0068] and [0070], and it sees no reason for restricting the claim with the doses illustrated in the examples. For instance, the application discloses the administration of the C19xCD3 bispecific single chain antibody at dose escalating steps from 5 to 60 µg/m^2/24h. The preferred dose of dexamethasone is between 6 and 40 mg, administered twelve hours and one hour before antibody administration but also one to three days after each dose of the antibody.

3.2.4 With regard to the generalisation of the NAEs observed in the examples to those recited in claim 1, the appellant-opponent has not provided any convincing argument why some NAEs would be prevented but not others.

3.3 Consequently, the board has no serious doubts that the skilled person can carry out the invention of claim 1 without undue burden. Therefore, claim 1 meets the requirements of Article 83 EPC.

4. Auxiliary request 4 - novelty (Article 54 EPC)

D5 is an international patent application with the same filing date as the patent in suit (27 October 2011) but an earlier priority date (27 October 2010). Therefore, the content of D5 can belong to the prior art under Article 54(3) EPC only if it enjoys the filing date of its priority application, D6.

The passage in D5 cited by the appellant-opponent as disclosing the subject-matter of claim 1 of auxiliary request 4 is paragraph [0141]. Although an equivalent paragraph is missing from D6, the appellant-opponent contended that the same teaching could be derived from the following passages in D6:

- page 22, lines 22 to 34
- page 37, line 30 to page 38, line 2
- page 38, lines 13 to 21

The board agrees with the appellant-patent proprietor that the cited passages fail to disclose at least the administration of dexamethasone prior to the first dose of the antibody and prior to the second and/or the third dose of the antibody, as required by claim 1.

The parts of the cited passages on the co-administration of dexamethasone read as follows:

"*An example of a co-administered medicament or drug is a chemotherapeutic such as dexamethasone*" (page 22, lines 26 and 27)

"*Administration 'in combination with' one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order*" (page 22, lines 33 and 34)

"*In a preferred embodiment, dexamethasone is administered together with the CD19xCD3 bispecific antibody. Specifically, dexamethasone is administered during the increase of the first, second and/or third dosis of the CD19xCD3 bispecific single chain antibody*" (page 37, lines 30 to 33)

"*Preferably, when dexamethasone is administered during the increase of the dosis of the CD19xCD3 bispecific antibody between the first and second period or between the second and third period of time, respectively, as described herein, it is administered at day n-3, n-2, n-1, n, n+1, n+2 and/or n+3, wherein n is the last day of the first or second period of time, respectively, and wherein the maximum amount of days during day n-3 and n+3 is 3, 4 or 5 days, with 3 or 4 days being preferred*" (page 38, lines 13 to 18)

The passages on page 22 and the first line of the passage on page 37 contemplate the possibility of co-administering dexamethasone with the antibody. This encompasses the possibility of pre-administration, simultaneous administration and post-administration. However, the passages do not refer to co-administration with the first dose of the antibody. The passages on pages 37 and 38 disclose co-administration of dexamethasone during the increase of the first, second and/or third doses, which encompasses co-administration before the second and/or the third doses. Therefore, the cited passages do not clearly and unambiguously disclose that dexamethasone is administered prior to the first dose in addition to prior to the second and/or the third dose of the antibody.

It follows that paragraph [0141] of D5 does not belong to the prior art and that the subject-matter of claim 1 of auxiliary request 4 is novel (Article 54 EPC).

5. *Auxiliary request 4 - priority (Article 87 EPC)*

The appellant-patent proprietor contended that the subject-matter of claim 1 was clearly and unambiguously

derivable from a general reading of the priority application D30.

The board disagrees. D30 does not disclose that dexamethasone is administered prior to the first and prior to the second and/or the third dose of the CD19xCD3 bispecific single chain antibody, let alone with a prophylactic aim. According to the passages cited by the appellant-patent proprietor, the administration of the glucocorticoid accompanied or preceded that of the CD3 binding domain (page 5, lines 11 and 12) or it was prior, concurrent and/or subsequent (page 6, lines 20 and 21 and page 15, lines 10 and 11). The example on page 19, lines 5 to 7 is the only passage in which dexamethasone was clearly administered as prophylaxis before the first dose of CD3 binding domain. However, this example does not disclose other features of claim 1 such as the administration before the second and/or the third dose of the antibody or that the second dose exceeds the first dose.

Therefore, claim 1 does not enjoy the priority date of D30, meaning that document D8 belongs to the prior art under Article 54(2) EPC and can be used for the assessment of inventive step.

6. Auxiliary request 4 - inventive step starting from D2

6.1 Document D2 (page 1, first paragraph and claim 1) is concerned with the treatment of forms of lymphoma and leukaemia with C19xCD3 bispecific single chain antibodies. It deals (page 2, second paragraph and page 18, second paragraph) with the infusion-related side effects associated with T-cell activation, such as the cytokine release syndrome. These side effects are

hypotension, pyrexia, fatigue, vomiting, tachycardia, hypertension, headache and back pain.

D2 teaches (paragraph bridging pages 17 and 18 and page 21, second paragraph) that infusion-related adverse events can be prevented by administering the antibody in low amounts as a long-term continuous infusion. In addition, a glucocorticoid can be co-administered to suppress the inflammation caused by cytokine production at the initial phase of the infusion (page 27, last paragraph). Example 5 of D2 discloses the treatment of two patients with a CD19xCD3 bispecific single chain antibody administered by long-term continuous infusion. The patients received an initial exposure dose of 5 µg/m^2/24h and a maintenance dose of 15 µg/m^2/24h continued for two or four weeks. The patients also received methylprednisolone one hour before starting the treatment to suppress the cytokine release at the initial phase of the infusion.

6.2 It was common ground between the appellants that the subject-matter of claim 1 differs from the teaching of D2, in particular Example 5, in the glucocorticoid and the administration of the glucocorticoid before the second and/or the third dosage of the antibody.

6.2.1 The appellants disputed whether the NAEs of claim 1 constitute an additional distinguishing feature. The appellant-opponent argued that the NAEs of claim 1 belonged to the adverse events associated with the cytokine release dealt with in D2. It noted that the appellant-patent proprietor (statement of grounds of appeal, paragraph 53) and D31 (paragraph bridging pages 7 and 8) had explained that the cause of the NAEs of claim 1 was associated with the migration of activated T-cells into the tissues. The same explanation was

given in D2 (page 18, second paragraph) for the occurrence of the adverse events associated with the cytokine release. Furthermore, like cytokine release adverse events, NAEs occurred immediately after infusion (D39, pages 56 and 57, Figures 2 and 3). Therefore, the NAEs of claim 1 were not different from those dealt with in D2, and they were prevented by the prophylactic administration of a glucocorticoid in Example 5 of D2.

6.2.2 This argument is not convincing. D2 does not refer to NAEs, let alone to the NAEs recited in claim 1. The passages in D2 cited by the appellant-opponent focus on the undesirable side effects associated with T-cell activation, in particular the cytokine release syndrome. In relation to the co-administration of a glucocorticoid, D2 (page 27, last paragraph and Example 5) explicitly teaches that it is aimed at suppressing cytokine production in the initial phase of the infusion period. There is no evidence on file that the skilled person would have understood from reading D2 that NAEs according to claim 1 would be encompassed by the side effects dealt with in D2. The board notes that the appellant-patent proprietor's submissions and the content of D31 and D39 do not constitute common general knowledge that the skilled person had in mind when reading D2. D31 is a patent application and does not qualify as common general knowledge, while D39 and the appellant-patent proprietor's submissions do not belong to the prior art. Furthermore, considering that NAEs occur in only 20 to 30% of patients (see above point 3.2.2, last paragraph), it cannot be concluded that the treatment given to two patients in Example 5 of D2 necessarily prevented the occurrence of NAEs.

In contrast, the patent shows in the reference tests in paragraphs [0077] to [0082] that, contrary to the side effects of D2, the NAEs recited in claim 1 do not (only) occur immediately after infusion of the antibody but also days later. In paragraphs [0077] to [0082], patients were treated with a continuous intravenous infusion of blinatumomab at escalating doses of 5, 15 and/or 60 µg/m^2/d, and NAEs (apraxia, tremor, speech disturbance and paresis) never occurred earlier than three days after treatment start.

6.2.3 Therefore, the board agrees with the appellant-patent proprietor that the NAEs of claim 1 are not necessarily infusion-related and that they constitute a distinguishing feature over D2.

6.3 The technical effect produced by the three differences identified above is that NAEs occurring during the treatment of patients with a CD19xCD3 bispecific single chain antibody are prevented or reduced, including the NAEs arising at later stages of the treatment. This effect was demonstrated in the examples in paragraphs [0085] and [0092] of the patent, which illustrate treatments according to claim 1.

Paragraph [0085] discloses a clinical trial on five lymphoma patients treated with blinatumomab continuous infusion at escalating doses of 5 µg/m^2/d (first week), 15 µg/m^2/d (second week) and 60 µg/m^2/d (subsequent two to six weeks). Each patient received a prophylactic dose of 20 mg dexamethasone twelve hours and one hour before the start of the treatment and before each dose increase. The fifth patient received an additional prophylactic dose of prednisolone one hour before the start of the infusion. None of the patients had to discontinue the treatment due to NAEs.

Paragraph [0092] discloses three treatments of lymphoma patients with blinatumomab at escalating doses of 5 µg/m^2/d (first week), 15 µg/m^2/d (second week) and 60 µg/m^2/d (until treatment end). In the first treatment, a cohort of six patients was treated with 100 mg prednisolone one hour before blinatumomab infusion, and one patient suffered a reversible NAE. In the second treatment, 8 mg doses of dexamethasone were administered one hour before infusion start and on days 1, 2 and 3. One of the two first patients treated suffered a reversible NAE, so the treatment was modified to a schedule according to claim 1: five patients received 20 mg dexamethasone at twelve to six hours and one hour before infusion start and before each dose escalation step and 8 mg doses in each of the following two days. None of the patients experienced NAEs.

Although the data and the number of patients treated in these clinical trials are limited, the board, on the basis of a balance of probabilities, is satisfied that the dosage regimen proposed in claim 1 for the administration of the CD19xCD3 bispecific single chain antibody and dexamethasone is indeed suitable to prevent the occurrence of the NAEs recited in claim 1. This was acknowledged when discussing sufficiency of disclosure (point 3.2 above).

6.3.1 Considering this technical effect, the appellant-patent proprietor formulated the objective technical problem as preventing further adverse events caused by the administration of a CD19xCD3 bispecific single chain antibody. The appellant-opponent denied the presence of a technical effect and formulated the problem in terms of an alternative, namely the provision of alternative

means for improving the tolerability of the administration of a CD19xCD3 single chain antibody.

Taking into consideration the parties' proposals and the technical effect recognised above, the board formulates the objective technical problem as the provision of means for improving the tolerability of the administration of a CD19xCD3 bispecific single chain antibody.

6.3.2 The board is satisfied that the subject-matter of claim 1 solves the objective technical problem (see point 3.2 above). Furthermore, the solution proposed in claim 1 is not obvious.

D2 proposes improving the tolerability of a CD19xCD3 bispecific single chain antibody by continuous infusion at escalating doses of the antibody, optionally with the prophylactic administration of a glucocorticoid one hour before infusion. D2 does not suggest using dexamethasone as the glucocorticoid. It is also silent on the administration of the glucocorticoid before infusion start and before the second and/or the third dose, and on the prevention of adverse events occurring at later stages of the treatment, in particular NAEs.

The combination of D2 with D17 or D22 does not render the subject-matter of claim 1 obvious, either. D17 and D22 contain information on the pharmacokinetics, dosing and therapeutic uses of glucocorticoids, including methylprednisolone and dexamethasone, but they do not suggest any possible use for preventing NAEs.

In the written appeal proceedings, the appellant-opponent had also relied on the combination of D2 with D41b to contest inventive step. However, the appellant-

opponent withdrew that argument at the oral proceedings before the board.

6.4 Therefore, the board concludes that the subject-matter of claim 1 of auxiliary request 1 is not obvious when inventive step is assessed starting from D2.

7. Auxiliary request 4 - inventive step starting from D8

7.1 D8 (page 1, first paragraph) discloses a dosage regimen for administering a CD19xCD3 bispecific antibody to a patient having a B:T cell ratio of 1:5 or lower. The dosage regimen comprises administering a first dose for a first period of time and, consecutively, a second dose for a second period of time, with the second dose exceeding the first. This regimen ameliorated or prevented adverse events caused by the administration of the antibody, in particular the NAEs that occurred mainly during the first days of treatment, such as seizures, encephalopathy, cerebral oedema, aseptic meningitis and headache (page 2, third and fourth paragraphs; page 5, line 16 to page 6, line 2; page 12, first and second paragraphs).

According to D8 (page 38, lines 14 to 16), "*Blinatumomab has a favorable safety profile with the exception of a subset of patients developing neurological adverse events (AEs) during the first days of treatment, such as confusion, speech impairment or cerebellar symptoms*". Nevertheless, after one week of treatment, the patient in Example 7 of D8 experienced a strong headache, mild tremor, apraxia, slow mental state and mild speech impairment. The adverse effects were treated with dexamethasone to their complete resolution, but a recurrent difficulty to play the guitar remained during the rest of the treatment.

7.2 The appellants did not dispute that the subject-matter of claim 1 differs from D8 in that dexamethasone was administered prior to the first and prior to the second and/or third doses of the antibody. Neither did they dispute that, if sufficiency of disclosure was acknowledged, this difference reduced the occurrence of NAEs (board's preliminary opinion, point 9.5).

7.3 The appellant-opponent agreed with the objective technical problem as formulated by the opposition division, namely providing an alternative method for reducing NAEs in CD19xCD3 bispecific single chain antibody treatment of lymphoma patients. However, considering that the technical effect produced over D8 is a reduced occurrence of NAEs, the objective technical problems should be formulated as starting from D2, i.e. the provision of means for improving the tolerability of the administration of a CD19xCD3 bispecific single chain antibody.

7.4 The appellant-opponent (statement of grounds of appeal, points 5.7.3 and 5.7.4) argued that, starting from D8 and seeking to solve the objective technical problem, the skilled person would turn to documents dealing with the reduction of infusion-related side effects arising from antibody therapy, in particular D34/D34a or D20.

However, neither D34/D34a nor D20 discloses the administration of dexamethasone prior to the first and prior to the second and/or the third dose of the antibody. Therefore, for this reason alone, the subject-matter of claim 1 is not obvious starting from D8 as the closest prior art.

8. Auxiliary request 4 - inventive step starting from D34/D34a

With its statement of grounds of appeal, the appellant-opponent raised for the first time an inventive-step objection starting from document D34/D34a as the closest prior art. In its preliminary opinion (point 4, last paragraph), the board indicated that it was minded to hold the objection inadmissible under Article 12(4) RPBA 2007. At the oral proceedings before the board, the opponent withdrew this objection.

9. Therefore, the board concludes that the subject-matter of claim 1 of auxiliary request 4 involves an inventive step and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated