Internal distribution code:

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

Datasheet for the decision of 30 July 2019

Case Number: T 0363/18 - 3.3.04

Application Number: 09002504.0

Publication Number: 2055313

IPC: A61K39/395, A61P35/02

Language of the proceedings: EN

Title of invention:
Treatment of hematologic malignancies associated with circulating tumor cells using chimeric anti-CD20 antibody

Patent Proprietor:
Biogen Inc.

Opponents:
Richter Gedeon Nyrt.
Pfizer Inc.(opposition withdrawn)
Novartis Pharma AG
Teva Pharmaceutical Industries Ltd
Sandoz AG
Genmab A/S
Celltrion, Inc.
Mundipharma International Ltd.

Headword:
Treatment of hematologic malignancies/BIOGEN

Relevant legal provisions:
EPC Art. 76(1)

Keyword:
All requests - claim 1 - added subject-matter (yes)

Decisions cited:
G 0001/05, G 0001/06, G 0002/10, T 0889/96, T 0099/13

Catchword:
-

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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

Case Number: T 0363/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 30 July 2019

Appellant: (Patent Proprietor)	Biogen Inc. 225 Binney Street Cambridge MA 02142 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent I: (Opponent 1)	Richter Gedeon Nyrt. Gyömröi út 19-21 1103 Budapest (HU)
Representative:	Neuefeind, Regina Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent III: (Opponent 3)	Novartis Pharma AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Pfister-Fu, Yixin Novartis Pharma AG Patent Department 4002 Basel (CH)
Respondent IV: (Opponent 4)	Teva Pharmaceutical Industries Ltd 5 Basel Street 49131 Petach-Tikva (IL)
Representative:	dompatent von Kreisler Selting Werner - Partnerschaft von Patent- und Rechtsanwälten mbB Deichmannhaus am Dom

Bahnhofsvorplatz 1
50667 Köln (DE)

Respondent V: (Opponent 5)
Sandoz AG
Lichtstrasse 35
4056 Basel (CH)

Representative:
Roth, Carla
König-Szynka-Tilmann-von Renesse
Patentanwälte Partnerschaft mbB
Mönchenwerther Straße 11
40545 Düsseldorf (DE)

Respondent VI: (Opponent 6)
Genmab A/S
Bredgade 34E
1260 Copenhagen K (DK)

Representative:
J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

Respondent VII: (Opponent 7)
Celltrion, Inc.
23 Academy-ro
Yeonsu-gu
Incheon 406-840 (KR)

Representative:
Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

Respondent VIII: (Opponent 8)
Mundipharma International Ltd.
Unit 194
Cambridge Science Park
Milton Road
Cambridge CB4 0AB (GB)

Representative:
Care, Alison
Kilburn & Strode LLP
Lacon London
84 Theobalds Road
London WC1X 8NL (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted on 23 November 2017 revoking European patent No. 2055313 pursuant to Article 101(3)(b) EPC

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	M. Blasi

Summary of Facts and Submissions

I. The appeal of the patent proprietor (hereinafter "appellant") lies from the decision of the opposition division revoking European patent No. 2 055 313 with the title "*Treatment of hematologic malignancies associated with circulating tumor cells using chimeric anti-CD20 antibody*".

II. The patent was granted for European patent application No. 09 002 504.0, filed as a divisional application of European patent application No. 05 022 104.3, which, in turn, was filed as a divisional application of European patent application No. 99 960 232.9. The latter had been filed as an international patent application, published as WO 00/27428 (hereinafter referred to as "document D47").

III. The opposition division held in their decision that claim 1 of each request dealt with (main request and auxiliary requests 1 to 3) failed to comply with the requirements of Article 76(1) EPC.

IV. With their statement of grounds of appeal, the appellant submitted sets of claims of a new main request and a new auxiliary request 1. Claim 1 of each of these requests was identical to claim 1 of the main request and auxiliary request 1 dealt with in the decision under appeal, which were themselves resubmitted and renumbered as auxiliary requests 2 and 3, respectively. The sets of claims of auxiliary requests 2 and 3 underlying the decision under appeal were resubmitted and renumbered as auxiliary requests 4 and 5, respectively.

Claim 1 of the main request and each of auxiliary requests 2 and 4 were hence the same and read:

"1. Use of an anti-CD20 antibody comprising human gamma 1 constant regions in the manufacture of a medicament for treatment of chronic lymphocytic leukemia (CLL) in a human patient, wherein the medicament is for administration to the human patient at a dosage of 500 to 1500 mg/m^2, and wherein the anti-CD20 antibody is rituximab."

Claim 1 of each of auxiliary requests 1, 3 and 5 were hence also the same and read:

"1. Use of an anti-CD20 antibody comprising human gamma 1 constant regions in the manufacture of a medicament comprising a therapeutically effective amount of the anti-CD20 antibody for treatment of chronic lymphocytic leukemia (CLL) in a human patient, wherein the medicament is for administration to the human patient at the therapeutically effective dosage amount of 500 to 1500 mg/m^2, and wherein the anti-CD20 antibody is rituximab." (Emphasis added by the board to indicate the difference from claim 1 of the main request)

V. Replies to the appeal were filed by four of the eight opponents (hereinafter referred to as "respondent I" to "respondent VIII"), i.e. by respondents II, V, VII and VIII.

VI. The board, after having accelerated the appeal proceedings as requested by the appellant and respondent II, summoned the parties to oral proceedings.

VII. Respondent II subsequently withdrew its opposition.

VIII. In a communication pursuant to Article 15(1) RPBA, the board expressed the preliminary opinion that the decision under appeal was correct as regards the finding that claim 1 of all the then pending requests (see section III) did not comply with the requirements of Article 76(1) EPC, *inter alia* because of the intermediate generalisation of the dosage feature "500 to 1500 mg/m^2". Consequently, the board envisaged considering each claim request submitted with the statement of grounds of appeal to be not allowable.

IX. At the oral proceedings the appellant and respondents V and VII were present. At the end of the oral proceedings the chair announced the decision of the board.

X. The appellant's arguments, in as far as they are relevant for the decision, can be summarised as follows (for ease of reference the reproduced arguments refer to document D47; see section II, above, and point 3, below).

Divisional application - added subject-matter (Article 76(1) EPC)

Main request and auxiliary requests 2 and 4 - claim 1

Amendments not infringing the requirements of Article 76(1) or 123(2) EPC could be made within the limits of what a skilled person would derive directly and unambiguously from the whole of the respective document as filed, using common general knowledge, and seen objectively and relative to the date of filing. Particular reference was made to decision G 2/10, for

this so-called "gold standard" in relation to added subject-matter, to decision T 99/13 for the "disclosure test" (see points 2.3 and 2.4), and to decision T 889/96 for the principle that a product designed for a particular use can be claimed as such (see points 2.1 and 2.2).

The person skilled in the art for the present invention was a practising oncologist with experience in the treatment of haematologic malignancies, such as chronic lymphocyte leukaemia (CLL).

Example 3 of document D47 disclosed, besides a particular treatment schedule, two medicaments, i.e. a first medicament of 375 mg/m^2 of rituximab and a second medicament of between 500 and 1500 mg/m^2 of rituximab. For the skilled person it was directly and unambiguously evident that the first medicament was used, as indicated, for minimising infusion-related side effects, and the second for actually treating CLL. The latter medicament was a key and indispensable tool within any desired treatment schedule to achieve, by a single specific dose, the therapeutically effective treatment of CLL as claimed. The medicament could be administered as many times as desired by treating physicians.

The disclosure of the particular dose of a medicament, i.e. a product, in the treatment of a disease could establish the basis for a second medical use claim for this product. In fact, claim 1 of all requests was not related to a treatment schedule, but was a purpose-limited product claim for a medicament that was a therapeutically effective single specific dose of rituximab.

Document D47 disclosed to the skilled person on page 1, lines 7 to 10, that the invention was directed to the treatment of haematologic malignancies associated with high numbers of circulating tumour cells by the administration of "*a therapeutically effective amount*" of a chimeric or humanised anti-CD20 antibody. This task was also referred to on page 2, lines 17 to 24, page 3, line 10 and page 4, lines 3 to 6, using rituximab in the treatment of CLL. It was thus an explicit objective of the invention to determine a therapeutically effective single specific dose of a chimeric or humanised anti-CD20 antibody, rituximab being the particularly preferred anti-CD20 antibody (page 5, lines 14 to 22), independent of how (i.e. in which regimen) the therapeutically effective amount of the antibody was used.

Example 3 disclosed: i) a particular dose of rituximab "*to minimize infusion-relapsed side effects*" (page 10, lines 21 and 22) which could be used as such, i.e. independent of any treatment regimen; ii) a medicament in the form of a single specific dose of rituximab of 500 to 1500 mg/m^2 (page 11, line 2) which could be used as such, i.e. independent of any treatment regimen; and iii) a treatment regimen involving the previous two, all three in the context of treating CLL patients.

The example thus provided the skilled person with the particulars of the "*therapeutically effective amount*" of a chimeric or humanised anti-CD20 antibody referred to throughout the description in the treatment of CLL, i.e. a medicament of 500 to 1500 mg/m^2 of rituximab. Particular examples of this range of doses

were disclosed on page 11, lines 11 to 13, i.e. 500, 560, 650 and 825 mg/m^2.

The fact that the determined and identified therapeutically effective single specific dose of rituximab was administered several times in the experiments disclosed in example 3 (page 11, lines 1 and 2) did not detract from the fact that the determination of the dose as such was a significant and important contribution made by the inventors.

Formulating the claims of all the requests as a medicament for the treatment of CLL containing rituximab at a dosage of 500 to 1500 mg/m^2 therefore did not amount to an intermediate generalisation of the disclosure of example 3.

Auxiliary requests 1, 3 and 5 - claim 1

No particular arguments in addition to those for claim 1 of the main request and each of auxiliary requests 2 and 4 (identical to each other) were submitted for defending claim 1 of each of auxiliary requests 1, 3 and 5 (identical to each other).

XI. The respondents' arguments, in as far as they are relevant for the decision, can be summarised as follows (for ease of reference the reproduced arguments refer to document D47; see section II, above, and point 3, below).

Divisional application - added subject-matter (Article 76(1) EPC)

All requests - claim 1

The main request contravened Article 76(1) EPC because the earliest application, document D47, failed to disclose the therapeutic use as claimed.

A dosage of 500 to 1500 mg/m^2 was solely disclosed in example 3 of document D47 in the context of the specific embodiment wherein "*increased dose levels*" of 500 to 1500 mg/m^2 were used as part of a complex stepped-up dosage regimen for the treatment of CLL.

The claims merely referred to that dosage of 500 to 1500 mg/m^2; they did not recite all the other features of the originally disclosed stepped-up dosage regimen for rituximab. The amendment amounted to an unallowable intermediate generalisation from the disclosure in example 3 of document D47, because the skilled person was presented with new information that was not disclosed in the application as filed (see case law on intermediate generalisations in Case Law of the Boards of Appeal of the EPO, 8th edition 2016, pages 439 to 444).

The stepped-up dosage regimen of example 3 for the treatment of CLL required, for providing the claimed therapeutic effect, the combination of i) the administration of a first rituximab dose of 375 mg/m^2 by infusion, followed by ii) three "*subsequent*" weekly, increased rituximab dosages of between 500 and 1500 mg/m^2, wherein iii) all of these subsequent dosages remained the same. Therefore, the following features were essential to the core teaching of

example 3: (a) a stepped-up dosage regimen involving the administration of a first dosage of 375 mg/m^2 prior to the administration of the dosage of 500 to 1500 mg/m^2; the repeated weekly administration of the subsequent dosage of 500 to 1500 mg/m^2, and (b) the particular mode of administration of the doses, i.e. by infusion.

Example 3 failed to disclose that the administered doses, individually, provided the claimed therapeutic effect in the treatment of CLL. Thus, example 3 did not provide a direct and unambiguous disclosure basis that made it possible to refer- in isolation - to the administration of a dosage of 500 to 1500 mg/m^2 for the treatment of CLL. Hence, example 3 did not directly and unambiguously disclose a "medicament" for the treatment of CLL as contended by the appellant. The word "medicament" in claim 1 was only there for wording reasons.

XII. The appellant requested at the end of the oral proceedings that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request, or alternatively, of one of the sets of claims of auxiliary requests 1 to 5, all filed with the statement of grounds of appeal.

Respondents V and VII requested at the end of the oral proceedings that the appeal be dismissed.

The same was requested in writing by the remaining parties to the appeal proceedings, except by respondent III who did not make any submissions in the appeal proceedings.

Reasons for the Decision

1. The appeal is admissible. In view of their withdrawal of the opposition, respondent II ceased to be a party to the appeal proceedings as regards substantive issues. Other issues for which respondent II might have remained a party to the proceedings did not arise in the present case.

2. The duly summoned respondents I, III, IV, VI and VIII did not attend the oral proceedings. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the board continued the proceedings in these parties' absence and they were treated as relying on their written submissions, if any.

Divisional application - added subject-matter (Article 76(1) EPC)

3. The board concurs with the opposition division - and the parties to these appeal proceedings have not contested - that the disclosure of the earlier application for the European patent application underlying the patent in suit (see section II) are identical. Therefore, if a basis can be identified in document D47 for a particular feature in a claim, the requirements of Article 76(1) EPC are fulfilled for that claim in respect of this feature (see also decision G 1/06, OJ EPO 2008, 307, Headnote).

4. As the appeal has been dismissed for the reasons given below, the board has assumed, for the purpose of this decision and in the appellant's favour, albeit without hearing the parties and deciding on this issue, that the dose unit "mg/m^3" could be corrected to read

"mg/m^2" in the text of example 3 of the description without infringing Article 123(2) EPC (see in particular points 10 and 11, below).

Main request and auxiliary requests 2 and 4 - claim 1

5. The claim, which is in the "Swiss-type" second medical use format, is for the use of rituximab (an anti-CD20 antibody comprising human gamma 1 constant regions) in the manufacture of a medicament for the treatment of chronic lymphocytic leukaemia (CLL) in a human patient, wherein the medicament is for administration to the human patient at a dosage of 500 to 1500 mg/m^2.

6. Accordingly, the subject-matter of the claim is defined by the particular combination of three distinct main features, each addressing other technical aspects, namely i) the active compound rituximab; ii) the therapeutic treatment of CLL in a human patient and iii) the particular dosage of 500 to 1500 mg/m^2 of rituximab.

7. The subject-matter of a divisional application must be directly and unambiguously derivable from the earlier application as filed (see decision G 1/06, *supra*), thus document D47 here, as determined by the totality of its claims, description and figures when read in context. Furthermore, because the wording of Article 76(1) EPC and Article 123(2) EPC is so similar (in all three languages of the EPC), the same principles apply for both provisions when determining whether subject-matter extends beyond the content of an (earlier) application as filed (see decisions G 1/05 and G 1/06, OJ EPO 2008, 271 and 307, point 5.1 of the Reasons).

8. The board concurs with the appellant that amendments are allowable under Articles 76(1) and 123(2) EPC within the limits of what a skilled person can derive directly and unambiguously from the whole of the documents as filed, using common general knowledge, and seen objectively and relative to the date of filing. This is also referred to as the "gold standard", a term coined in decision G 2/10 (OJ EPO 2012, 376, point 4.3 of the Reasons).

9. In the case in hand, therefore, it was assessed whether the "gold standard" referred to above could be considered satisfied by the disclosure of document D47 in respect of the subject-matter of the claim (see point 5).

10. It was undisputed that the sole disclosure of a dosage of 500 to 1500 mg/m^2 of rituximab in document D47 is in example 3 with the title "*Phase I/II Study of RITUXAN® in CLL*". The relevant parts of example 3 read:

"*In an attempt to maximize activities in CLL we are conducting a Phase I/II study.* ***All patients receive a first dose of 375 mg/m^3 to minimize infusion-relapsed*** **[sic]** ***side effects. Subsequent weekly dosages (3) remain the same but are given at an increased dose level.*** *Sixteen patients have been treated at dosages of 500-1500 mg/m^3. Medium age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Medium white blood cell count was 40 x 10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75 x 10^9/L (range, 16-160), median β_2 immunoglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mgm^3* [sic]*);*

another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m^3 dose level has been fully evaluated. ***Eight patients have completed therapy*** *(4 at 500 mg/m^3, 3 at 650 mg/m^3, 1 at 825 mg/m^3). One patient treated at 560 mg/m^3 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.*" (Emphasis added by the board)

11. In relation to the units used for the dose (document D47 in fact discloses the dose unit **mg/m^3**, see point 4, above), the board accepts, for the sake of the argument, that a skilled person would derive directly and unambiguously from the disclosure in example 3 of document D47 the particular dosage of 500 to 1500 mg/m^2 of the active compound rituximab, i.e. aspects i) and iii) referred to in point 6, above.

12. The board considers that example 3 discloses the use of the particular dose of 500 to 1500 mg/m^2 of rituximab *in the explicit context of* a sequence of administration by infusion of four doses of rituximab for the therapeutic treatment of human CLL patients, the first dose given being a particular and lower one than the three subsequent doses in the range of 500 to 1500 mg/m^2 (see parts emphasised in bold in text reproduced in point 10). Thus, the administration of rituximab in a specific amount followed by increased, identical amounts within a specific range, at a specified frequency (weekly) and for a certain duration (four doses), forms part of the dosage regimen described in example 3.

13. The board is, however, unable to identify in example 3 the disclosure of aspect ii) of the definition of the claimed subject-matter (see point 6, above, i.e. the aspect "*treatment of CLL in a human patient*" as referred to in general in the claim) in particular in combination with aspect iii) (i.e. the particular dosage of 500 to 1500 mg/m^2 of rituximab). Indeed, example 3 discloses dosages of rituximab of 500 to 1500 mg/m^2 in the context of a particular therapy of human CLL patients, characterised by four administrations of the active compound in a stepped-up regimen (see point 12). This is, however, different from disclosure of a treatment of CLL in a human patient by the sole dose of 500 to 1500 mg/m^2 of rituximab.

14. The appellant argued, by reference to a number of paragraphs in document D47, that it had been the explicit task of the invention to determine a useful "*therapeutically effective amount*" of a chimeric or humanised anti-CD20 antibody, here rituximab, in the treatment of, *inter alia*, CLL, and that example 3 identified the useful single specific dose of rituximab as this "*therapeutically effective amount*", i.e. 500 to 1500 mg/m^2 of rituximab. This justified the wording of the claim under Article 76(1) EPC.

15. The board accepts that the passages referred to by the appellant in the description of document D47 (i.e. page 1, lines 7 to 10; page 2, lines 17 to 24; page 3, line 10 and page 4, lines 3 to 6) refer in general to the administration of a therapeutically effective amount of an anti-CD20 antibody, such as rituximab, for the treatment of diseases like CLL. The board, however, is unable to see how the skilled person would have inferred, directly and unambiguously, from these

passages that it was the dosage of rituximab of 500 to 1500 mg/m^2, as mentioned in example 3, which constituted - alone and as such - the therapeutically effective *amount*. In fact, the total amount of the therapeutically effective doses of rituximab administered to the patients as disclosed in example 3, i.e. the four sequential administrations in the regimens of example 3, does not fall within this range. The board cannot therefore see any basis in the passages referred to by the appellant for aspect ii), let alone for a combination of aspects ii) and iii) of claim 1 (see point 6).

16. In view of the above considerations, the board concludes that the combination of the claimed features (see point 5) was not what a skilled person derived directly and unambiguously from example 3 of document D47 and the whole of the documents as filed, using common general knowledge and seen objectively and relative to the date of filing.

17. The board's conclusion is not contrary to any of the principles set out in the decisions T 889/16 of 22 September 1999 and T 99/13 of 14 January 2016, to which the appellant has referred to when introducing the relevant principles governing the examination of the requirements of Article 76(1) and 123(2) EPC. That in those cases the competent board reached the conclusion that the claimed subject-matter did not extend beyond the content of the (earlier) application as filed resulted from the circumstances of the individual cases.

18. Accordingly, the board holds that claim 1 of the main request and each of auxiliary requests 2 and 4 does not comply with the requirements of Article 76(1) EPC.

Auxiliary requests 1, 3 and 5 - claim 1

19. As compared to claim 1 of the main request, this claim now defines the medicament for treatment of CLL to comprise the therapeutically effective dosage amount of rituximab of 500 to 1500 mg/m^2.

20. No particular arguments in addition to those for claim 1 of the main request and each of auxiliary requests 2 and 4 were submitted for defending claim 1 of each of auxiliary requests 1, 3 and 5. The board holds that its considerations and conclusions on claim 1 of the main request in relation to the requirements of Article 76(1) EPC also apply to this claim, all the more in view of the fact that a single dose of rituximab of 500 to 1500 mg/m^2 has no support in the passages referred to by the appellant (see point 15).

21. The board concludes, therefore, that claim 1 of each of auxiliary requests 1, 3 and 5 equally does not comply with the requirements of Article 76(1) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated