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# Datasheet for the decision of 16 April 2019

**Case Number:** T 1481/16 - 3.3.04

**Application Number:** 07855983.8

**Publication Number:** 2119452

**IPC:** A61K39/00, C07K16/28

**Language of the proceedings:** EN

**Title of invention:**
Pharmaceutical composition, comprising an anti-CD6 monoclonal antibody used in the diagnosis and treatment of rheumatoid arthritis

**Applicant:**
Centro de Inmunologia Molecular

**Headword:**
Anti-CD6 monoclonal antibody/CENTRO DE INMUNOLOGIA MOLECULAR

**Relevant legal provisions:**
EPC Art. 56, 83, 84, 123(2)

**Keyword:**
Main request - EPC requirements met (yes)

**Decisions cited:**

**Catchword:**

-

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**Case Number: T 1481/16 - 3.3.04**

# D E C I S I O N
# of Technical Board of Appeal 3.3.04
# of 16 April 2019

| | |
|---|---|
| **Appellant:** (Applicant) | Centro de Inmunologia Molecular<br>Calle 216 esq. 15, Atabey<br>Playa, Ciudad de la Habana, AP. 16040<br>Ciudad de la Habana 12100 (CU) |
| **Representative:** | Schmitz, Georg<br>Kanzlei Huber & Schüssler<br>Truderinger Strasse 246<br>81825 München (DE) |
| **Decision under appeal:** | **Decision of the Examining Division of the European Patent Office posted on 7 January 2016 refusing European patent application No. 07855983.8 pursuant to Article 97(2) EPC.** |

**Composition of the Board:**

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|---|---|
| **Chairwoman** | G. Alt |
| **Members:** | B. Claes |
| | P. de Heij |

## Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division refusing European patent application No. 07 855 983.8. The application has the title "*Pharmaceutical composition, comprising an anti-CD6 monoclonal antibody used in the diagnosis and treatment of rheumatoid arthritis*".

II. The examining division held that claims of a main request and five auxiliary requests lacked, *inter alia*, clarity (Article 84 EPC), related to added subject-matter (Article 123(2) EPC), and/or concerned subject-matter which lacked inventive step (Article 56 EPC).

III. With the statement of grounds of appeal the applicant (hereinafter "appellant") submitted claims of a new main request and new auxiliary requests and argued in favour of compliance with the requirements of Articles 56, 84 and 123(2) EPC.

IV. In a communication pursuant to Article 15(1) RPBA, the board expressed its preliminary opinion that claim 1 of all the requests lacked clarity (Article 84 EPC). The board furthermore expressed concerns relating to the compliance of claims of the requests with the requirements of Articles 56 and 123(2) EPC.

V. With a letter responding to the board's communication, the appellant submitted claims of a new main request and two auxiliary requests.

VI. Oral proceedings were held as scheduled. At the end of the oral proceedings the appellant upheld one sole (main) claim request and the chair announced the decision.

The sole claim of the main request read:

"1. A pharmaceutical composition for use in the treatment of Rheumatoid Arthritis, comprising as active principle a monoclonal antibody that recognizes the human leukocyte differentiation antigen CD6, wherein said monoclonal antibody is a humanized antibody T1h, and wherein said humanized antibody T1h is obtained by genetic engineering methods from the secreting hybridoma IOR-T1A with deposit No. ECACC 96112640 and wherein the composition is administered to a patient as a weekly dose of the humanized antibody T1h during 6 weeks in a dose selected from the group consisting of 0.2, 0.4, 0.6 and 0.8 mg/KG of body weight and wherein the humanized antibody T1h comprises a heavy chain having a variable region with the following sequence: Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser;
and
a light chain having a variable region with the following sequence: Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu

Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala."

VII. The following documents are referred to in this decision:

D2: US 6,572,857

D10: Montero *et al.* (2002), Arthritis Research, 4, Suppl. 1, Abstracts of the 22nd European Workshop for Rheumatology Research, Abstr. 114.

VIII. The appellant's arguments in relation to the sole claim of the main request can be summarised as follows:

*Article 123(2) EPC*

Support for the claim was provided in the application as filed, in particular in Example 1.

In the last sentence on page 2 and the sentence spanning pages 3 and 4, the application as filed explicitly cross-referenced document EP-A-0 807 125, which disclosed the humanised anti-human CD6 monoclonal antibody T1h having particular disclosed and claimed amino acid sequences (see claim 4 of the document). The sequences present in claim 1 thus found a basis in the application as filed.

The claim thus complied with the requirements of Article 123(2) EPC.

*Inventive step (Article 56 EPC)*

The claimed subject-matter differed from the treatment disclosed in document D10, which represented the closest prior art for the assessment of inventive step, in that the composition now comprised a humanised antibody and was administered once a week at a lower dose.

The claimed composition solved the problem to provide for a more convenient and effective therapy that was safer and reduced the risk of adverse effects as compared to the composition disclosed in document D10.

The claimed subject-matter was not obvious to the skilled person considering the disclosure in document D10 taken alone or read in conjunction with the disclosure in document D2, the latter document disclosing the humanised monoclonal antibody (mAb) as defined in the claim in the treatment of psoriasis. Indeed, even if the skilled person combined the teachings of documents D10 and D2, this would not provide a reasonable expectation of success that the particular humanised antibody could successfully be used in the treatment as specified in the claim.

The claimed subject-matter thus involved an inventive step (Article 56 EPC).

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the sole claim of the main request.

## Reasons for the Decision

1. The appeal is admissible.

*Amendments (Article 123(2) EPC)*

2. The board is satisfied that the claimed subject-matter finds a basis in the application as filed, in particular in Example 1 disclosing the long-lasting therapeutic effect of the humanised monoclonal antibody T1h - a particular humanised form of the mouse anti-human CD6 monoclonal antibody ior-t1 - after administration to 13 patients suffering from rheumatoid arthritis (RA).

3. The amino acid sequences of the variable heavy and light chain regions characterising the humanised T1h monoclonal antibody according to claim 1 are not disclosed in the application as filed. They are however identical to those of the humanised antibody disclosed and claimed in claim 4 in document EP-A-0 807 125, i.e. a document explicitly cross-referenced in the last sentence on page 2 and in the sentence spanning pages 3 and 4 of the application as filed, disclosing this particular antibody for use in the invention. These passages read respectively as follows: "*Subsequently, based on methods of genetic engineering (Patent No. 0699755 E.P. Bul.) it was obtained a humanized version of this mouse anti-human CD6 monoclonal antibody designated T1h (EP 0 807 125A2)*" and "*The humanized anti-human CD6 monoclonal antibody T1h is obtained from the secreting hybridoma IOR-T1A with deposit No. ECACC 96112640, as described in (EP 0 807 125A2)*".

4. In view of this disclosure in the application, the board considers the amino acid sequence of the antibody T1h as being contained within the disclosure content of the application as filed by means of the cross-reference. Indeed, the two above-mentioned passages describe a monoclonal antibody (mAb) by its name, the name of a hybridoma secreting it and its respective deposit number - all information also referred to in claim 1 to characterise the antibody referred to therein. Furthermore, both passages identify the European patent application in which this information is disclosed by its publication number, and said information is unambiguously linked to an amino acid sequence which is the one now referred to in claim 1.

5. In view of the above considerations, the board is satisfied that the claim complies with the requirements of Article 123(2) EPC.

*Clarity (Article 84 EPC)*

6. The amendments to the claim have rendered the concerns of the board in relation to clarity, expressed in the communication pursuant to Article 15(1) RPBA and the oral proceedings in relation to earlier claims, moot. The board accordingly holds that the claim complies with the requirements of Article 84 EPC.

*Sufficiency of disclosure (Article 83 EPC)*

7. The board is satisfied that the application as filed, in particular in Example 1 and the data summarised in Figure 1, demonstrates the suitability of the pharmaceutical composition as claimed for the treatment of rheumatoid arthritis patients. The requirements of Article 83 EPC are thus complied with.

*Novelty (Article 54) EPC*

8. The claimed subject-matter is novel as the use of the antibody referred to in the claim for the treatment of rheumatoid arthritis was not disclosed in the cited prior art. The requirements of Article 54 EPC are thus complied with.

*Inventive step (Article 56 EPC)*

*Closest prior art*

9. The disclosure in document D10, a scientific abstract, represents the closest prior art for the assessment of inventive step in accordance with the problem-solution approach.

10. Document D10 discloses therapeutic immunosuppression in human patients suffering from RA with the murine anti-CD6 monoclonal antibody (mAb) "ior t1". The antibody recognises a different epitope on human CD6 as compared to other known anti-CD6 mAbs and has demonstrated therapeutic effects in psoriasis vulgaris (see for examlple title and lines 14 and 15; see also page 2, lines 31 to 33 of the application as filed).

11. Document D10 discloses in particular a phase II clinical trial (PIICT) with the murine ior t1 mAb for treatment in 18 RA patients. A therapeutic dose-finding study based on seven consecutive daily doses at 0.2 mg/kg, 0.4 mg/kg or 0.8 mg/kg of murine mAb was conducted with intravenous infusion. Clinical evaluation and analysis were performed weekly. The 0.4 mg/kg dose of the antibody was defined as the Optimum Biological Dose, with a long-lasting clinical improvement observed

in this group. This intravenous treatment reduced the number of tender and swollen joints starting on day four of the infusions. The abstract concludes with the statement that: "*This is the first clinical report supporting the relevance of the CD6/CD6-ligand model as a potential target for rheumatoid arthritis immunotherapy. A PI-IICT with a humanized version for iort1* [sic] *mAB is underway*" (see last four lines of document D10).

*Technical effect, problem and solution*

12. The claimed subject-matter differs from the RA treatment regime disclosed in document D10, firstly, in that instead of the murine ior t1 mAb, the claim refers to a particular humanised form of this mAb, named T1h, which recognises the same epitope on human CD6 and is defined by specific amino acid sequences of the variable heavy and light chain regions.

13. The technical effect of this difference is that the mAb satisfies the continuous need in human immunotherapy to provide therapeutic antibodies variants that demonstrate a minimum of immunogenicity upon administration in humans whilst maintaining the therapeutic effects of the original (non-human) variant (humanisation).

14. Secondly, the particular humanised mAb also allows, for a weekly administration of substantially lower amounts of antibody, as compared to the daily administration disclosed for the murine mAb, to obtain a therapeutic effect. Indeed, the weekly dose of the murine ior t1 mAb administered in the therapeutic dose-finding study of the phase II clinical trial disclosed in document D10 (see point 10, above) amounts to 1.4 (7 x 0.2), 2.8

(7 x 0.4) and 5.6 (7 x 0.8) mg/kg, respectively. Further, it is disclosed that after four days of intravenous treatment with a daily dose of 0.4 mg/kg of the murine mAb, i.e. the Optimum Biological Dose for a long-lasting clinical improvement, the number of tender and swollen joints started to reduce. This thus corresponds to a weekly dose of at least 1.6 (4 x 0.4) mg/kg.

15. The humanisation of the antibody as well as the lower administered dose both reduce the risk of side effects, making the therapy safer. Accordingly, the board considers that the technical problem to be solved by the claimed invention is the provision of an effective therapy for human RA patients, based on mAbs, which is at the same time safer and has a reduced risk of adverse effects as compared to the therapy disclosed in document D10, i.e. the use of the murine ior t1 mAb.

*Obviousness*

16. As regards obviousness of the subject-matter of the claim, it needs to be established whether or not the proposed solution - here the use of the specific humanised antibody which allows for a weekly dose administration as low as 0.2, 0.4, 0.6 and 0.8 mg/kg of body weight - was obvious to the skilled person in the light of the available state of the art.

17. The board accepts, and the appellant has not argued differently, that the skilled person, without inventive effort, was in a position to provide humanised forms of the murine ior t1 disclosed in document D10 with the primary view of providing a safer antibody having a reduced risk for adverse effects in human patients, whilst maintaining the antibody's therapeutic effects

(see also last sentence of document D10 recited in point 9, above).

18. The board, furthermore, also accepts that an example of such a humanised form of the murine antibody - which also reads on the antibody referred to in claim 1, i.e. which similarly recognises human CD6 and has the particular amino acid sequences of the variable heavy and light chain regions - was explicitly known in the prior art and disclosed for example in document D2 (see claim 3) in the context of the treatment of psoriasis.

19. However, the board holds - and the board has seen no evidence to the contrary - that neither the teaching in document D10 considered on its own (which discloses as the lowest weekly dose for a clinical effect 1.4 mg/kg, administered in daily doses of 0.2 mg/kg; see point 13 above), nor document D10 considered in combination with the particular structural knowledge of the humanised antibody disclosed in document D2 (which was disclosed in the context of the therapy of psoriasis), suggested to the skilled person that the particular humanised antibody of the claim provides a successful treatment of human RA patients by allowing for a weekly dose administration as low as 0.2, 0.4, 0.6 and 0.8 mg/kg of body weight.

20. Therefore, and by applying the problem-and-solution approach, the board concludes that the claimed subject-matter involves an inventive step (Article 56 EPC).

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the following claims and a description and figures to be adapted thereto:

   - claim of the main request submitted during the oral proceedings on 16 April 2019.

The Registrar: The Chair:

D. Magliano G. Alt

Decision electronically authenticated