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Datasheet for the decision of 8 December 2016

Case Number: T 0652/12 - 3.3.04

Application Number: 08010046.4

Publication Number: 1972638

IPC: C07K16/28, A61K45/00, A61K39/395, A61P19/02

Language of the proceedings: EN

Title of invention:
Remedies for juvenile chronic arthritis and related diseases

Applicant:
Chugai Seiyaku Kabushiki Kaisha

Headword:
Treatment for systemic onset juvenile idiopathic arthritis/ CHUGAI

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main request (no)

Decisions cited:
T 0385/07, T 0790/12

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Case Number: T 0652/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 8 December 2016

Appellant: (Applicant)	Chugai Seiyaku Kabushiki Kaisha 5-1 Ukima 5-chome Kita-ku Tokyo 115-8543 (JP)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 4 November 2011 refusing European patent application No. 08010046.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against the decision of the examining division to refuse European patent application 08 010 046, entitled "*Remedies for juvenile chronic arthritis and related diseases*".

II. In the decision under appeal, the examining division held that the sole claim request before it did not meet the requirements of Article 56 EPC.

III. European patent application 08 010 046 is a divisional application of parent European patent application No. 02 708 772. The parent application itself was refused by an examining division and an appeal against that decision was filed and is dealt with by this board as case T 790/12. The statement of grounds of appeal for both cases is essentially identical.

IV. The following documents are relevant to this decision. For the sake of consistency, the same numbering is used in the present decision and in decision T 790/12.

D1: Mangge and Schauenstein, Cytokine, 1998, 10(6), 471-480

D14: Elliot el al., Br. J. Rheumatol., 1997, 36(5): 589-593

D16: De Benedetti and Martini, J. Rheumatol., 1998, 25(2), 203-207

D19: Yilmaz et al., Clin. Rheumatol., 2001, 20(1), 30-35

D25: De Benedetti and Ravelli, BioDrugs, 2000, 14(2), 93-98

D31: Grogan, K., "Roche files to get sJIA on RoActemra label", PharmaTimes (online) 18 October 2010

D32: European Medicines Agency Assessment Report for RoActemra (Procedure No. Type II variation EMEA/H/C/ 955/11/15)

D33: Declaration of Dr Thomas Lehman (including Exhibit A (CV) and Exhibits 1 to 26 cited therein)

V. Claim 1 of the main request, filed with the statement of grounds of appeal, reads:

"1. An interleukin-6 (IL-6) antagonist for use in the treatment of chronic arthritides diseases of childhood, wherein the IL-6 antagonist is a humanised monoclonal antibody against human IL-6 receptor and wherein the chronic arthritides diseases of childhood is systemic onset type juvenile rheumatoid arthritis in which symptoms can not be controlled with nonsteroidal anti-inflammatory drugs, long term bolus steroids and immunosuppressants".

Claims 2 to 5 of the main request are dependant on claim 1.

VI. The board issued a communication pursuant to Article 15(1) RPBA, setting out its preliminary appreciation of substantive and legal matters concerning the appeal.

VII. The appellant replied to the board's communication with a letter which was accompanied, *inter alia*, by documents D31 to D33.

VIII. The appellant's arguments relevant to the decision, given in writing and during the oral proceedings, may be summarised as follows:

Main (sole) request

Inventive step - Article 56 EPC

The issue to be determined in the appeal was the obviousness of using an anti-IL-6 receptor antibody for treating systemic onset type juvenile idiopathic arthritis (sJIA).

Claim 1 was for a humanised monoclonal antibody against human IL-6 receptor for use in the treatment of systemic onset type juvenile rheumatoid arthritis of childhood (sJIA). The inclusion in the claim of the features "*which can not be controlled with nonsteroidal anti-inflammatory drugs, long term bolus steroids and immunosuppressants*" reflected the inventor's finding, set out in working Example 1, that the claimed therapy represented a significant improvement over the therapies available before the relevant date of the application. The wording of the claim emphasised the fact that the invention represented the first effective treatment for sJIA.

At the date of the application, the skilled person would have been aware that:

i) systemic onset type juvenile rheumatoid arthritis of childhood (sJIA), was a subtype of (JIA);

ii) the condition of juvenile idiopathic arthritis (JIA) was characterised by a highly complex system of cytokine expression with each having overlapping regulatory functions. Several cytokines had been identified as playing an important role in sJIA but no one cytokine had been identified as causing it.

iii) while TNFα was one of the cytokines elevated in JIA and had been proposed as a potential target for its treatment, document D14 disclosed that targeting TNFα failed to effectively treat sJIA. The reduction in TNFα level in the sJIA patient of document D14 was accompanied by a concomitant reduction in the level of IL-6. Thus, the observation of an elevated IL-6 level in sJIA would not have been seen by the skilled person as predictive of whether its targeting would result in an effective treatment,

iv) document D25 contained a proposal to treat sJIA with etanercept, targeting both TNFα and TNFß. The skilled person reading this in the light of his knowledge of the art would have considered the effect of targeting TNFß as of equal, if not of greater importance, to the effect of targeting TNFα.

Closest prior art

In possession of the above background knowledge and in view of the claimed subject-matter, the skilled person would have regarded document D25 as closest prior art. It reported successful clinical trials of etanercept for treating some subtypes of JIA and was therefore a promising starting point for the skilled person looking for treatments for other subtypes, including sJIA.

The problem and its solution

Taking into account the claimed subject-matter and the teaching of the closest prior art, the technical problem to be solved was the provision of an effective therapy for systemic onset JIA. The term "*effective*" was used to emphasise the contrast to previous, less successful therapeutic attempts, such as the administration of the anti-TNFα antibody, cA2, disclosed in document D14.

In contrast to the closest prior art, the claimed subject-matter represented a real breakthrough in treating the terrible childhood disease sJIA.

Obviousness

The skilled person, starting from the disclosure of document D25, would have considered that etanercept represented the obvious solution to the above formulated problem. Document D25 taught that etanercept was the clear preference for treating sJIA because it neutralised both TNFα and TNFß, the latter of which was proposed as a major player in this disease. To arrive at the presently claimed subject-matter as a solution to the technical problem, the skilled person would have had to ignore the ultimate conclusion of the document that "*etanercept offers a promising alternative for patients who have persistently active arthritis despite treatment with methotrexate*".

Although document D25 did, in one section, mention that anti-IL-6 therapies may be effective in treating sJIA, this statement would not have led the skilled person to the claimed invention because it would have been perceived as merely reflecting the authors' particular

interest in the topic of the involvement of IL-6 in the disease (cf. document D16) and not as a promising potential treatment for sJIA. Indeed, the skilled person reading the whole disclosure of document D25 would have considered that the authors' optimism about therapies targeting IL-6 and its receptor was not supported by the evidence available at the time.

Moreover, the skilled person would have noted the reference on page 97, left column, to document D14. Here it was disclosed that the treatment of a patient with severe sJIA with infliximab (cA2), a chimeric mAb directed against human TNFα, caused a rapid and maintained decrease in circulating IL-6 (see Figure 2C) and resulted in a reduction of the systemic manifestations (i.e. fever) of the disease but failed to modify the severity of the arthritis.

This failure, in spite of lowered IL-6 level, would have significantly reduced the skilled person's expectation of success for IL-6 as a proposed therapeutic target.

Furthermore, the role of IL-6 in sJIA was unknown at the filing date, as reported for example in document D19 and confirmed by Dr Lehmann in his declaration (D33). In the absence of a definitive knowledge of the causation of sJIA (even after the filing date, see document D33, paragraph 15), the person skilled in the art at the time of filing could not have a reasonable expectation that the claimed treatment would be effective.

Decision T 385/07 supported the above inventive step analysis. In it, the competent board held that a document disclosing clinical trials of a compound did

not disclose information about its therapeutic efficacy.

In the present case there was not even a disclosure that clinical trials of a treatment for sJIA with neutralization of IL-6 by any means were under way, nor was there any detailed disclosure of the nature of any trials. Although document D25 stated that "*neutralisation of IL-6*" was under investigation, it contained no information about the agent involved.

IX. Oral proceedings before the board for this case and for case T 790/12 were held on 8 December 2016, with the proceedings for this case being adjourned until after the board had expressed its opinion in the parent case. At the end of the proceedings the Chairwoman announced the decision of the board.

X. The appellant's requests were that the decision under appeal be set aside and that a patent be granted on the basis of the request annexed to the decision of the examining division under "Annex A" (main request).

Reasons for the Decision

The invention

1. The invention concerns an antagonist monoclonal antibody against human IL-6 receptor for use in the treatment *of* systemic onset type juvenile rheumatoid arthritis of childhood.

2. Juvenile rheumatoid arthritis of childhood is also known in the art as juvenile idiopathic arthritis (JIA). "*JIA is the most common rheumatic disease of*

childhood [...]. It is a heterogeneous inflammatory disorder that is classified in different subtypes based on the clinical characteristics in the first 6 months of disease. Three principal types of onset are recognised (oligoarthritis, polyarthritis and systemic arthritis)" (see document D25, page 92, paragraph 1). The systemic onset sub-type of the disease (sJIA) is a chronic arthritis developing in children of less than 16 years of age (*ibid.* and the application, page 5, lines 4 to 12) that is characterised by a systemic onset, consisting in high-spiking fever, rheumatoid rash, hepatosplenomegaly and/or serositis (see document D1, page 472, paragraph 1).

Main (sole) request

Claim 1

3. Claim 1 is for an antagonist monoclonal antibody against human IL-6 receptor for use in the treatment of sJIA. The sJIA is further defined as a disease that cannot be controlled with any of nonsteroidal anti-inflammatory drugs, long term bolus steroids and immunosuppressants.

4. At oral proceedings the appellant explained that these latter features served to emphasize that the claimed invention represented the first truly effective therapy for sJIA. The board is therefore of the view that the skilled person would construe the claim as directed to an antagonist monoclonal antibody against human IL-6 receptor for use in the treatment of sJIA.

Inventive step - Article 56 EPC

Closest prior art

5. Document D25 discloses the use of etanercept, a fusion protein of a portion of a human soluble TNFα receptor and the Fc portion of a human antibody constant region, which acts by blocking the interaction between TNFα and β with their cell surface TNF receptors, for the treatment of JIA (see document D25, page 96, left column, section 2). The document provides a summary of the results of a clinical trail of etanercept on particular patients with polyarticular JIA (*ibid.*) and *inter alia* concludes that it (etanercept) represents an "*important addition to* [available] *treatments for JIA*, [...] *offering a promising alternative for patients who had persistently active arthritis despite treatment with methotrexate*" (*Id.*, page 97, final paragraph).

6. According to document D25 "[...] *methotrexate has become the therapeutic agent of choice for children with JIA who fail to respond adequately to NSAIDs. A number of studies have shown that methotrexate is an effective and well tolerated medication for the treatment of patients with JIA, with 60 to 70% of patients experiencing a significant clinical benefit with the standard dose regimen of 10 to 15 mg/m^2/week. Furthermore, preliminary evidence has been provided that methotrexate may significantly alter the natural history of JIA*" (see page 93, right column).

7. Thus, since sJIA patients fall within the overarching group of JIA patients, it is apparent that sJIA patients had been treated according to the above mentioned regimen.

8. The treatment of sJIA patients with methotrexate disclosed in document D25 is therefore regarded as the closest prior art for the presently claimed subject-matter.

The technical problem and its solution

9. The difference between the closest prior art, represented by document D25 and the claimed subject-matter lies in the molecule used and the focus on sJIA as the specific sub-type of JIA to be treated.

10. The claim further specifies that the sJIA, is such that its "*symptoms cannot be controlled with nonsteroidal anti-inflammatory drugs, long term bolus steroids and immunosuppressants*". These features reflect the information provided in "*Working Example 1*" concerning a 5-year-old male sJIA patient who, prior to therapy according to the invention, had been treated with aspirin, oral bolus administration of prednisolone, methyl-prednisolone pulse therapy and plasmapheresis, and furthermore the combined use of cyclosporin A. These features of the claim reflect the fact that at the effective date of the application, the existing pharmaceutical therapies did not provide a fully effective means of controlling the symptoms of the disease.

11. In view of these differences, the objective technical problem can be formulated as the provision of an effective agent for the treatment of sJIA.

12. As is generally the case where a therapeutic application is claimed, attaining the claimed therapeutic effect is a functional technical feature of

the claims (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, II.C.6.2).

Obviousness

13. The skilled person starting from the treatment of sJIA with methotrexate as disclosed in document D25 (representing the closest prior art) and seeking to solve the problem formulated above would have encountered in the same document, a section headed "*Future directions*" (see page 97) where, in relation to future therapies for sJIA, the following is disclosed: "[...] *a vast body of evidence points to prominent IL-6 production as playing a major role in systemic-onset JIA, therefore suggesting that anti-IL-6 therapies may be effective in this disease. The available experimental approaches to the specific neutralisation of IL-6, including a humanised anti-IL-6 receptor antibody and receptor antagonists, are under evaluation in preclinical and clinical settings*."

14. Since anti-IL-6 therapy with humanised anti-IL-6 receptor antibody is explicitly mentioned as a potential treatment for sJIA patients, the board considers that the above cited passage provided the skilled person with a direct incentive to consider treating sJIA patients with humanised anti-IL-6 receptor antibody as suggested.

15. The appellant has argued that the skilled person would not have reasonably expected that sJIA could be treated with an antagonist monoclonal antibody against human IL-6 receptor as claimed. A main line of argument in this regard was based on the disclosure in document D14 that the treatment of a 16-year-old female with a 12 year history of severe sJIA, with infliximab (cA2), a

chimeric mAb directed against human TNFα, did not modify the severity of the arthritis. In the appellant's view, the failure of infliximab to treat sJIA would have adversely affected the skilled person's expectations that therapies based in anti-IL-6 activity would be effective. Although document D14 reported that the sJIA patient treated with infliximab showed a "*rapid decrease" in IL-6 levels*" with maintenance of the response thereafter, neutralisation of IL-6 did not result in an improvement of sJIA.

16. The results disclosed in document D14 show that, in a single patient, down-regulation of IL-6 by means of an antibody directed to TNF*α* was able to control some of the symptoms of sJIA but did not result in any improvement of joint pain or tenderness. The authors could not explain why the sJIA patient did not respond as well to the therapy as adult rheumatoid arthritis (RA) patients, stating "*the reason for this difference is not known, and while any conclusions drawn from a single case must be considered tentative, the data may indicate that TNFα is a less important inflammatory mediator in the articular disease of systemic JCA than it is in adult RA. Alternatively, the explanation may lie in matters relating to the dose or scheduling of the cA2. It is noteworthy that even the systemic disease features were controlled for only about 10 days, despite treatment with a relatively high dose of cA2. The patient was catabolic, as evidenced by the significant weight loss she had experienced over the preceding 3 months, and it is possible that the administered cA2 was rapidly degraded as a result of her catabolic state*" (see page 592, final two paragraphs).

17. The board cannot agree with appellant's evaluation of the disclosure of document D14. In the board's view, the skilled person reading both the passage in document D25 concerning the potential of anti-IL6 therapies for treating sJIA and taking into account the disclosure of document D14 cited above, would not have been persuaded that anti-TNFα therapy was definitively incapable of improving joint pain or tenderness associated with sJIA. The skilled person would have noted that document D14 itself stated that the results reported were regarded as tentative since the study only involved a single patient and because the particular circumstances of that patient might have explained the observed results.

17.1 Furthermore, the skilled person would have evaluated the disclosure of document D14 in the context of the disclosure of document D25. The authors of document D25 were aware of and acknowledged the results reported in document D14 (see document D25, page 97, left column, final full paragraph) and nevertheless remained optimistic about the potential of anti IL-6 therapies for treatment specifically of sJIA. Indeed they noted that clinical evaluation of anti-IL-6 therapies, including of a humanised anti-IL-6 receptor antibody, were already under way (see Point 13 above). While the authors of document D25 had a demonstrated interest in the involvement of IL6 in sJIA (see for instance document D16), there is no evidence available to the board that supports the appellant's assertion that the authors of document D25 only mention IL-6 based therapy of sJIA because of personal bias. On weighing the evidence before it, the board concludes that the skilled person, having evaluated both the disclosure of document D14 and the disclosures of those documents leading to the hypothesis that sJIA is an IL-6 mediated

disease (see page 96, left column, second paragraph), would have considered that the expectation that therapy of sJIA based on neutralising IL-6 might succeed was reasonable.

18. In another line of argument, the appellant suggested that starting from document D25 as closest prior art and seeking to solve the above formulated technical problem, the skilled person would have been led to etanercept as a solution, this being the entire point of document D25.

19. The board recognises that document D25 is primarily concerned with giving an account of the potential of etanercept for the treatment of JIA. However, the question of whether etanercept, which is not an IL-6 binding antibody, provides an alternative solution to the technical problem is not an issue in considerations of obviousness of the claimed subject-matter. Moreover, the fact that, in an article whose main topic is the efficacy of etanercept in the treatment of JIA, the authors highlighted the potential of anti-IL-6 therapies specifically for sJIA, would in the board's view, have had significant positive impact on the skilled person's expectations with regard to the likely success of such therapies.

20. Similarly, the appellant's arguments relating to the fact that the prior art recognised IL-6 as one of several cytokines elevated in systemic onset JIA patients, but that no cytokine or its elevation had been identified as causing the disease, is not seen by the board as significantly weakening the expectation of success of the skilled person contemplating the claimed anti-IL-6 therapy for sJIA. There is no evidence available to the board that supports the idea that the

skilled person needed to know the definitive cause of sJIA before considering potential therapies. Indeed the evidence from document D25 shows that various therapies were under consideration (see point 13., above). Furthermore, the fact that more than one potential solution to the technical problem was available to the skilled person at the relevant date of the application need not necessarily reduce their expectation of success for any particular one of those solutions, especially if, as here, that expectation was based on concrete facts and evidence.

21. The appellant considered that conclusions reached in decision T 385/07 on the issue of expectation of success, should apply equally to the case at hand. At issue in that decision was the question of whether or not the anti-tumour activity of a drug against a certain cancer type established in a clinical trial was predictive of its anti-tumour activity in another cancer type (see Reasons, point 16). The present board cannot see that such considerations apply to the present case where the question to be answered does not concern the extrapolation of the therapeutic activity from one disease type to another, albeit related disease type. On the contrary none of the appellant's arguments succeeds in establishing that there were reasons for the skilled person not to take the pointer in document D25 seriously.

22. In view of the above considerations, the board concludes that the subject-matter of claim 1 lacks inventive step with regard to the disclosure of document D25.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated