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Datasheet for the decision of 2 October 2019

Case Number: T 0713/15 - 3.3.01

Application Number: 04807818.2

Publication Number: 1707215

IPC: A61K45/00, A61K39/395, A61P29/00, A61P9/00

Language of the proceedings: EN

Title of invention:
Remedy for vasculitis

Patent Proprietor:
CHUGAI SEIYAKU KABUSHIKI KAISHA

Opponent:
Ablynx N.V.

Headword:
Vasculitis/CHUGAI

Relevant legal provisions:
EPC Art. 100(b)
RPBA Art. 13

Keyword:
Grounds for opposition - insufficiency of disclosure (yes)
Late-filed auxiliary request 1 - admitted (no)

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Beschwerdekammern

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Case Number: T 0713/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 2 October 2019

Appellant: (Opponent)	Ablynx N.V. Technologiepark 21 9052 Ghent-Zwijnaarde (BE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	CHUGAI SEIYAKU KABUSHIKI KAISHA 5-1, Ukima 5-chome, Kita-ku Tokyo, 115-8543 (JP)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 February 2015 rejecting the opposition filed against European patent No. 1707215 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 1 707 215 is based on European patent application No. 04807818.2, filed as an international application published as WO 2005/061000.

Independent claims 1 and 14 of the patent as granted read as follows:

"1. An agent for use in preventing and/or treating vasculitis, said agent comprising an antibody against IL-6 receptor as an active ingredient, wherein the antibody inhibits the binding of IL-6 to the IL-6 receptor."

"14. The use of an antibody against IL-6 receptor for the manufacture of a preventive and/or therapeutic agent for vasculitis, wherein the antibody inhibits the binding of IL-6 to the IL-6 receptor."

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(47) T. Xenitidis et al., Rheumatology, 2013, 52, 1729-1731

(49) L. Cantarini et al., Clin. Rheumatol., published online on 15 April 2014, 3 pages

(50) A. Diamantopoulos et al., Rheumatology, 2013, 52, 1923-1924

(54) Declaration of Professor Charles Dickson Pusey, 8 October 2015, 70 pages (including annexes)

III. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

The opposition division rejected the opposition.

IV. The opponent (appellant) appealed this decision. In the statement setting out the grounds of appeal, the appellant provided arguments relating to novelty and sufficiency of disclosure. The issue of inventive step was briefly addressed.

V. In its reply to the grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed.

VI. Whith a letter dated 22 July 2019, the appellant submitted document (56) and provided arguments on novelty and inventive step.

VII. In a communication pursuant to Article 15(1) RPBA, the board indicated certain points to be discussed.

VIII. With a letter dated 11 September 2019, the respondent submitted auxiliary requests 1 to 7.

IX. Oral proceedings before the board took place on 2 October 2019. During the oral proceedings the respondent filed a new auxiliary request 1 and withdrew all other auxiliary requests.

Claim 1 of auxiliary request 1 reads as follows:

"1. An agent for use in preventing and/or treating vasculitis, said agent comprising an antibody against IL-6 receptor as an active ingredient, wherein the antibody inhibits the binding of IL-6 to the IL-6 receptor, wherein said vasculitis is polyarteritis nodosa or aortitis syndrome."

Claim 11 of auxiliary request 1 is based on claim 14 as granted and has been amended in an analogous manner.

X. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows.

Sufficiency of disclosure

Vasculitis was a term for various diseases with unknown causes and pathogenesis. The only link between the various diseases was the presence of inflammation. The patent in suit provided the teaching that IL-6 was involved in inflammation and was consequently a target when providing a treatment for this group of diseases. The only further information provided by the patent in suit were the reports on two patients. These patients were successfully treated. However, it had to be noted that these two patients were not typical. They represented extreme cases with manifestations which, untypically, did not respond to standard treatment. The expert declaration (54) did not reflect the knowledge available at the effective date of the patent in suit. It had been drafted in 2015 and represented the personal belief of the expert. Documents (47), (49) and (50) cast serious doubt on the teaching of the patent in suit that IL-6 inhibition therapy could be used to treat any type of vasculitis. Document (47) showed that such a therapy did not work in a patient suffering from

Takayasu's arteritis. Documents (49) and (50) provided evidence that the anti IL-6 receptor antibody did not treat all forms of Behçet's disease. In mucocutaneous Behçet's disease the administration of tocilizumab led to a worsening of mucocutaneous manifestations. Documents (49) and (50) linked this failure to a cytokine profile different from the cytokines in other forms of vasculitis, see document (49), page 3, left-hand column, end of first paragraph and document (50), page 1923, right-hand column, third paragraph. Consequently, there were certain forms of vasculitis that could not be treated by an anti IL-6 receptor antibody. Clinical trials were the only way to find out which forms or subforms of vasculitis were treatable. Performing clinical trials involved an undue burden.

Admission of auxiliary request 1

Auxiliary request 1 should not be admitted. Seeking to re-introduce claim requests that had been filed in the first instance proceedings but had not been maintained in appeal constituted a procedural abuse. A party's complete case had to presented with the grounds of appeal or the reply thereto. A party had to be prepared for the fact that the impugned decision might be overturned on appeal. Furthermore, auxiliary request 1 extended the scope of discussion and raised new issues.

XI. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows.

Sufficiency of disclosure

The patent in suit contained clinical data for two patients showing that vasculitis could be treated by

the administration of an anti IL-6 receptor antibody. One of the two examples of the patent in suit related to a patient having a type of vasculitis affecting large blood vessels, the other affecting small blood vessels. Dr Pusey, an expert in the field of vasculitis, declared that, in view of the examples of the patent in suit, it was plausible and scientifically reasonable to predict that different types of vasculitis might be treated with an anti IL-6 receptor antibody (see points 16 to 20 of document (54)). Furthermore, a marketing authorisation for tocilizumab had been granted. The burden of proof to show that an anti IL-6 receptor antibody could not be used to treat vasculitis thus rested with the appellant. However, the appellant had provided no evidence that the patent was not sufficiently disclosed. Only isolated failures had been mentioned. Document (49) related to a single patient whose treatment with tocilizumab was discontinued due to severe side effects (abstract). Document (50) reported that tocilizumab had been successfully administered in patients with Behçet's syndrome. Although the treatment had to be discontinued due to side effects in the two patients of document (50), it was noted that at least a partial response was seen in patient 2 (page 1923, paragraph bridging the columns). No medicament, even when approved, worked for all patients. The lack of efficacy in isolated patients due to toxicity could not lead to a finding of insufficiency.

Admission of auxiliary request 1

The opposition division had maintained the patent in suit based, *inter alia*, on a positive finding of sufficiency of disclosure. It had thus not been necessary to file a set of claims comprising the

restrictions made in auxiliary request 1 at an earlier time. Auxiliary request 1 contained only simple amendments based on the incorporation of the subject-matter of dependent claims. Furthermore, it was a *bona fide* attempt to overcome the issues derived from the reasoning given on sufficiency of disclosure.

XII. The final requests of the parties as far as relevant to the present decision were as follows:

The appellant requested that:
-the decision under appeal be set aside and that the patent be revoked;
-documents D57 and D59, filed by the respondent with its letters dated 11 September 2019 and 16 September 2019 respectively, not be admitted into the proceedings.
The appellant withdrew the request (mentioned in its letter dated 22 July 2019) for admission of document D56 into the proceedings.

In addition the appellant requested that auxiliary request 1, filed by the respondent at the oral proceedings of 2 October 2019, not be admitted into the proceedings;

The respondent requested that the appeal be dismissed or, alternatively, that the patent be maintained on the basis of auxiliary request 1, filed during the oral proceedings of 2 October 2019.

Reasons for the Decision

1. Any reference in this decision to the RPBA concerns RPBA 2007.

2.

3. The appeal is admissible.

4. *Sufficiency of disclosure*

4.1 The patent in suit relates to a novel preventive and/or therapeutic agent for vasculitis (paragraph [0001]).

According to paragraph [0005] intensive and extensive research led the inventors to demonstrate that IL-6 was indispensable in the pathology of vasculitis. It was found surprisingly that when the binding of IL-6 to its receptor was inhibited by an IL-6 receptor antibody IL-6 *per se* was decreased in the blood. Thus, IL-6 inhibition not only had an anti-inflammatory effect on vasculitis but also treated vasculitis *per se* by acting on the core of vasculitis.

Paragraph [0005] relates to vasculitis in general and does not distinguish between various types of vasculitis.

No further mechanistic explanation is provided in the patent in suit. However, the clinical data of patients having either aortitis syndrome, also called Takayasu's arteritis, or arteritis nodosa show that the treatment of certain types of vasculitis by anti IL-6 receptor antibody which inhibits the binding of IL-6 to the IL-6 receptor leads to a marked improvement in patients' conditions.

4.2 The appellant has provided arguments that the effect, the prevention and/or treatment of vasculitis, would not be achieved for all types of vasculitis. The subject-matter of claim 1 of the main request was thus not sufficiently disclosed over the whole scope of

claim 1.

In order to substantiate this argument, the appellant has referred, *inter alia*, to documents (49) and (50). According to the appellant, these documents showed that certain forms of vasculitis, in particular mucocutaneous Behçet's disease/syndrome, could not be treated by an anti IL-6 receptor antibody.

The respondent has argued that it could not be understood from documents (49) and (50) that the treatments were not effective at all. In fact, the treatments were stopped due to side effects. A lack of efficacy in isolated patients due to toxicity could not lead to a finding of lack of sufficiency of disclosure.

4.3 A detailed analysis of documents (49) and (50) is thus necessary.

Document (49) reports in its abstract that a patient diagnosed with Behçet's disease experienced a paradoxical mucocutaneous flare following tocilizumab (an anti IL-6 receptor antibody inhibiting binding of IL-6 to IL-6 receptor) administration, which worsened after the second infusion. The authors of document (49) considered this to be an acute exacerbation of the disease (page 2, left-hand column, second paragraph). It is said that different cytokine clusters might be involved and that a treatment based on IL-6 antagonism may cause imbalances in the cytokine network (page 3, left-hand column, first paragraph). In their conclusion, the authors of document (49) hypothesise that, although favourable responses can be obtained with tocilizumab in neuro-Behçet's disease (see titles of references [10], [20] and [25]), the attempt to manage mucocutaneous lesions by blocking IL-6 leads to

a worsening of the disease (page 3, last paragraph).

Document (50) relates to the "Lack of efficacy of tocilizumab in mucocutaneous Behçet's syndrome: report of two cases" (title). It starts off by describing that Behçet's syndrome is a rare multisystem inflammatory disease that presents clinically with mucocutaneous, ophthalmic, neurological, joint and vascular manifestations (page 1923, left-hand column, first paragraph). Studies on two patients with genital and mouth ulcers showed a deterioration of the mouth and/or genital ulcers. The first patient experienced the worsening of her condition already after the first infusion of tocilizumab. The second patient, after showing a partial response to the treatment, developed painful genital ulcers which had to be treated with high doses of opioid analgesics and corticosteroids (page 1923, paragraph bridging the columns). The authors of document (50) considered that their patients failed to respond to the treatment. They state that their report of the failure of patients to respond to the treatment with tocilizumab is in contrast to others that describe the efficacy of tocilizumab for severe neurological and ocular Behçet's syndrome (page 1923, right-hand column, second paragraph). Document (50) then goes on to speculate that mucocutaneous Behçet's syndrome had a different cytokine profile from other phenotypes of Behçet's syndrome, such as for example neurological and ocular Behçet's syndrome (page 1923, right-hand column, paragraph 3).

From the disclosure of documents (49) and (50) it can be taken that a specific type of Behçet's disease, i.e. Behçet's disease with mucocutaneous manifestations or phenotype, cannot be treated with an anti IL-6 receptor antibody. These two documents also find that not only

no treatment but a worsening of the manifestations of the disease occurs. The authors of these documents class the symptoms occurring after administration of tocilizumab as manifestations of mucocutaneous Behçet's disease. They do not identify the occurring symptoms as side effects. Furthermore, these two documents address the question of cytokine profiles and potential differences in these profiles between different types of Behçet's disease. Both documents question whether the mere blocking of IL-6 would address issues relating to the pathogenesis of mucocutaneous Behçet's disease. Document (50) in particular expresses its doubts in an extremely clear manner: "It was hypothesized that there are clusters of disease expression in BS [Behçet's syndrome] with different pathogenic mechanisms and response to treatment with different agents" (page 1923, right-hand column, last paragraph).

The discussion of cytokine profiles by the authors of documents (49) and (50) shows that the patients discussed in these documents are not seen as representing isolated failures.

There is thus evidence on file that inhibiting the binding of IL-6 to IL-6 receptor by an anti IL-6 receptor antibody does not lead to a prevention or treatment of every type of vasculitis.

4.4 In sum, the relevant facts relating to sufficiency of disclosure are the following.

The patent in suit provides indications on a mechanism of action for vasculitis in general and data for patients having two specific forms of vasculitis.

There is however evidence on file, in the form of

documents (49) and (50), that the claimed treatment does not work for all types of vasculitis.

It has thus been shown that the general mechanism postulated, which has led to a therapy relying on IL-6 inhibition, does not allow each and every form of vasculitis to be treated. The application as filed does not provide any form of guidance as to which types of vasculitis respond to the administration of an anti IL-6 receptor antibody. There is thus no teaching in the application as filed on how to treat vasculitis in all its forms. As a consequence of these findings, the subject-matter of claim 1 of the main request is not sufficiently disclosed over the whole scope of the claim.

4.5 Having come to this conclusion, it is not necessary to discuss document (47).

4.6 Two further arguments have been brought forward by the respondent:

Firstly, the respondent has referred to the expert declaration (54). There, Professor Pusey comes to the conclusion that based on the clinical data of the patent in suit, and possibly on two further post-published documents (see point 20 of document (54)), it was plausible and scientifically reasonable to predict that different types of vasculitis may be treated with an anti IL-6 receptor antibody. However, Professor Pusey neither mentions nor discusses the data of documents (49) and (50). In the absence of any appraisal of these documents, the expert declaration cannot provide crucial input on the issue of sufficiency of disclosure.

Secondly, the respondent has pointed to the fact that a marketing authorisation had been granted for tocilizumab. However, the marketing authorisation does not concern the treatment of vasculitis in general or the treatment of Behçet's disease. The granting of a marketing authorisation for particular diseases that are distinct from Behçet's disease cannot change the findings of point 2.4 above.

4.7 In view of the finding of lack of sufficiency of disclosure, it is not necessary to provide a reasoning for novelty of the main request.

5. *Admission of auxiliary request 1*

According to the Rules of Procedure of the Boards of Appeal (RPBA), appeal proceedings in *inter partes* cases are based on the statement(s) of grounds of appeal and the reply/replies of the other party/parties, subject to further conditions (Article 12(1),(4) RPBA). The admission of subsequent submissions (requests, facts or evidence) representing an amendment to a party's case is at the discretion of the boards (Article 114(2) EPC and Article 13 RPBA). This discretion has to be exercised appropriately, requiring the boards to consider all relevant factors, taking into account the specific circumstances of the case. Examples of criteria to be taken into consideration by the boards when exercising their discretion include the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy (confer Article 13(1) RPBA). These criteria are not exhaustive, and the boards have also considered aspects such as the reasons for the new submission or the extent of the amendments.

Auxiliary request 1 was filed at a very advanced stage of the appeal proceedings, namely at the oral proceedings before the board and after the discussion of sufficiency of disclosure of the main request. The board does not consider that a new situation had arisen during the oral proceedings which might justify the filing of this request. The fact that a board, on the basis of arguments presented by a party, might take a different view than the department whose decision is appealed, can not be considered a surprising event as it is one of the two possibilities. As the patent proprietor is the party that is solely responsible for determining the text of the patent (see Article 113(2) EPC), it is however obliged to submit amendments or possible fall-back positions. For reasons of procedural economy and fairness to the other party this must be done at the earliest possible opportunity.

In the present case, the respondent waited until after a negative finding of sufficiency of disclosure, a ground of opposition that was an issue throughout the opposition and appeal proceedings, before submitting auxiliary request 1. In view of the fact that sufficiency of disclosure had been a major issue in the appellant's case, the filing of auxiliary request 1 during oral proceedings before the board was contrary to procedural economy.

Consequently, in view of the extremely late state of the proceedings and the need for procedural economy, the board did not admit auxiliary request 1 into the proceedings (Article 13(1) and (3) RPBA).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated