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**Datasheet for the decision
of 30 March 2009**

Case Number: T 0021/07 - 3.3.04

Application Number: 00900306.2

Publication Number: 1143997

IPC: A61K 38/17

Language of the proceedings: EN

Title of invention:

Tumor necrosis factor antagonists and their use in
endometriosis treatment

Patentee:

Laboratoires Serono SA

Opponent:

Centocor, Inc.

Headword:

Endometriosis/SERONO

Relevant legal provisions:

EPC Art. 54, 56, 83, 123(2)

Keyword:

"Admissibility of appeal (yes)"
"Added matter (no); sufficiency of disclosure, novelty,
inventive step (yes)"

Decisions cited:

T 0019/90, T 0435/91, T 0646/92, T 0219/01

Catchword:

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Case Number: T 0021/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 30 March 2009

Appellant: Centocor, Inc.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 31 October 2006
rejecting the opposition filed against European
patent No. 1143997 pursuant to Article 102(2)
EPC 1973.

Composition of the Board:

Chair: U. Kinkeldey
Members: G. Alt
D. S. Rogers

Summary of Facts and Submissions

- I. This is an appeal by the opponent (appellant) against the decision of the opposition division to reject the opposition according to Art. 102(2) EPC 1973 against the European patent no. 1143997. The patent had been filed as International application no. PCT/IB00/00052 (published as WO 0043031) and has the title "Tumor necrosis factor antagonists and their use in endometriosis treatment".
- II. The opposition was based on Article 100(a) EPC on the grounds of lack of novelty and lack of inventive step, on Article 100(b) EPC on the ground of insufficiency and on Article 100(c) EPC on the ground of added subject-matter.
- III. Claims 1 and 2 as granted read:
- "1. Use of a TNF antagonist together with a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition for the treatment and/or prevention of endometriosis, wherein said TNF antagonist is a sequestering antagonist or a signalling antagonist.
2. Use of a TNF antagonist together with a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition to improve the implantation and fertility rate by reducing endometriotic lesions, wherein said TNF antagonist is a sequestering antagonist or a signalling antagonist. "

The set of claims further contained claims 3 to 12 dependent on claims 1 and 2.

- IV. The appellant requested that the decision of the opposition division be set aside and the patent be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed either because it was formally inadmissible and/or for substantive reasons.

Both parties requested oral proceedings as an auxiliary measure.

- V. The board summoned for oral proceedings to be held on 21 January 2009.

With a letter dated 06 January 2009 the appellant informed the board that it would not appear at the oral proceedings.

With the letter dated 14 January 2009 the respondent withdrew the request to schedule oral proceedings concerning the question of admissibility of the appeal. The request was maintained in case that the board should not be in a position to decide the issues of patentability in favour of the respondent on the basis of the written submissions.

The parties were informed by letter dated 15 January 2009 that the oral proceedings were cancelled.

- VI. The following documents are cited in the present decision:

- D1: Dorland's Illustrated Medical Dictionary, W.B. Saunders Company - ed. 28, pages 89-90
- D2: American Journal of Reproductive Immunology, 1990, vol. 24, pages 45-50, Mori, H. et al.
- D3: Human Reproduction, 1997, vol. 12, no. 9, pages 2046-2050, Balasch, J. et al.
- D4: Fertility and Sterility, 1993, vol. 59, no. 6, pages 1196-1201, Zhang, R. et al.
- D5: Fertility and Sterility, 1988, vol. 50, no. 4, pages 573-579, Eisemann, J. et al.
- D6: Ann. J. Obstet. Gynecol., 1997, vol. 176, no. 3, pages 593-597, Harada, T. et al.
- D7: Mol. Human Repr., 1996, vol. 2, no. 1, pages 40-45, Arici, A. et al.
- D8: Biochemical and Biophysical Research Communications, 1988, vol. 155, no. 3, pages 1230-1236, Strieter, R.M. et al.
- D10: British Journal of Obstetrics and Gynaecology, 1995, vol. 102, Suppl. 12, pages 4-7, Gleicher, N.
- D11: WO 92/16553
- D12: The Lancet, Oct. 1994, vol. 344, pages 1125-1128, Elliott, M. et al.

D13: MIMS, Feb. 2004, Boehringer Ingelheim, pages 146-147

D22: Am. J. Obstet.Gynecol., 1986, vol. 155, no. 5, pages 1109-1113, Hahn, D.W. et al.

D32: Fertility and Sterility, 2004, vol. 81, pages 775-779, Barrier, B. F. et al.

D33: Hum. Reprod., 2006, vol. 21, no. 7, pages 1-7, Falconer, H. et al.

D43: Immunology, 1994, vol. 83, pages 262-267, Neuner, F. et al.

Declaration by Dr. Cornillie dated 9 August 2006

VII. In the following "TNF- α " will be abbreviated as "TNF".

VIII. The appellant's arguments may be summarized as follows:

Amendments (Article 123(2) EPC)

It was only disclosed in the application as filed that TNF sequestering and signalling antagonists were used in combination with a further active agent to improve implantation and fertility rate. Therefore, the use according to claim 2 of these antagonists alone extended the content of the application as filed.

Sufficiency of disclosure (Article 83 EPC)

The data of Table II of the patent did not provide evidence for an effective endometriosis treatment with

the antagonist TNF-RI, a soluble TNF receptor. Firstly, it was not credible that data obtained in rats could be extrapolated to humans. Secondly, the reduction of the size of endometriotic foci after two days was not statistically significant. Moreover, the experiment lacked a proper control group since the data for the sham-operated rats was not indicated.

Even if it was accepted that Table II made it plausible that TNF-RI would be effective in the treatment of endometriosis, they were however no proof that each of the antagonists referred to in the claim 1 was effective. Decisions G 2/88, T 94/82 and T 435/91 supported this view.

Finally, there was no data at all on the effect of the TNF antagonists referred to in the claims on the implantation and fertility rate. Therefore the invention according to claim 2 was not sufficiently disclosed.

Novelty (Article 54 EPC)

Document D1 defined an antagonist as "a substance that tends to nullify the action of another". Document D2 disclosed the use of danazol for the medical management of endometriosis and also that the compound suppressed the activity of TNF.

Document D3 disclosed the administration of pentoxifylline to infertile women suffering from endometriosis. Document D3 itself and also documents D8 and document D43 disclosed that pentoxifylline down-regulated TNF.

Thus, both danazol and pentoxifylline were TNF antagonists and therefore the disclosure in documents D2 and D3 destroyed the novelty of the subject-matter of claim 1.

Inventive step (Article 56 EPC)

The subject-matter of the claims lacked an inventive step in view of either of documents D2, D3, D4, D5, D6, D7 or D10 alone or in view of document D10 in combination with documents D11 to D13.

It was known that danazol and pentoxifylline down-regulated TNF-activity (see the section "Novelty" above). A skilled person would therefore immediately recognize that other compounds with a similar effect, for example known TNF antagonists such as TNF sequestering or signalling antagonists, would also be useful for the treatment of endometriosis and the related infertility. The subject-matter of claims 1 and 2 therefore lacked an inventive step over the disclosure in document D2 or D3.

Document D4 disclosed an in vitro assay demonstrating that the adherence of endometrial stromal cells to mesothelial cells was increased by the addition of TNF-alpha in a dose-dependent manner. The skilled person would have deduced from this result that the reduction of TNF levels would prevent adherence of endometrial cells and therefore endometriosis. It was obvious to use known TNF antagonists for this purpose.

Document D5 reported a correlation between inter alia the presence of extensive endometriosis and the incidence of elevated levels of TNF in the peritoneal fluid. The document even disclosed an in vitro experiment where an anti-TNF antibody blocked the TNF-mediated lysis of cells. Therefore, it was not only obvious in view of the disclosure in document D5 to reduce TNF levels for the treatment of endometriosis, but also that this could be achieved with TNF antagonists such as anti-TNF antibodies.

Document D6 taught that there was a relationship between endometriotic lesions and increased levels of the cytokines TNF and IL-6 in peritoneal fluid and concluded that TNF might have a key role in controlling cytokine synthesis in the peritoneal environment of endometriosis. Thus, also this document suggested to treat endometriosis by reducing TNF levels by using the known TNF antagonists,

The disclosure in document D7 of the use of TNF-neutralizing IgG antibodies to nullify the effect of TNF in the context of endometriosis research deprived claims 1, 2 and 11 of an inventive step.

Document D10 suggested that non-specific immune modulators were useful in the treatment of endometriosis. The skilled person knew that danazol, described and used in document D10, was such a compound. Since this compound fell under the definition of TNF sequestering and signalling antagonists according to claim 1 (see section "Novelty" above), the subject-matter of all claims lacked an inventive step in view of the disclosure in document D10 alone.

Moreover, document D10 disclosed that compounds used for the treatment of autoimmune diseases such as rheumatoid arthritis were likely candidates for the treatment of endometriosis. Document D11 disclosed monoclonal anti-TNF antibodies, in particular the specific antibody cA2, for the treatment of rheumatoid arthritis. Documents D12 and D13 underlined the usefulness of this antibody, which is also known under the name infliximab or the trade mark name Remicade for the treatment of rheumatoid arthritis. Hence, a combination of the teachings of document D10 with that in either of documents D11 to D13 rendered the claimed subject-matter obvious.

IX. The respondent's arguments may be summarized as follows:

Admissibility of the appeal

The appellant's grounds of appeal almost exclusively consisted of passages copied from three written submissions made during the opposition proceedings. The grounds of appeal were therefore a mere reference to previously filed submissions. According to the case law such a mere reference was not sufficient to substantiate an appeal.

Amendments (Article 123(2) EPC)

Claim 16, page 6, lines 26 to 28 and page 18, lines 19 to 24 of the application as filed provided an explicit basis for claim 2 which therefore complied with Article 123(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

The results provided in Table II and the corresponding Figure 1 of the patent in suit showed that the TNF antagonist exemplified in the patent, a soluble TNF receptor I reduced the size of endometriotic foci. These data indicated that this compound was useful for the treatment of endometriosis. Given that the treatment relied on the concept of blocking TNF activity either by neutralizing the epitope responsible for receptor binding or by interfering with the signalling cascade activated by TNF, one example was sufficient to make it credible that all TNF antagonists referred to in claims 1 and 2 could reduce the size of the endometriotic foci. Therefore, the disclosure in the patent was sufficient for the whole breadth of the claims.

Moreover, post-published documents D30 to D34 confirmed that TNF antagonists falling under the definition according to claims 1 and 2 were effective and thus were evidence that it was reasonable to generalize the results.

Since infertility was a consequence of endometriosis, the disclosure in the patent was also sufficient to enable the skilled person to carry out the subject-matter of claim 2.

Novelty (Article 54 EPC)

Neither danazol nor pentoxifylline fell under the definition of a sequestering or signalling antagonist according to the patent. Therefore, documents D2 and D3

did not destroy the novelty of the subject-matter of claim 1.

Inventive step (Article 56 EPC)

Document D2 disclosing danazol for the treatment of endometriosis was the closest prior art document. The skilled person would not have considered the suppression of TNF or its signalling pathway as a basis for a successful treatment for endometriosis in view of any of documents D2 to D7, D10 alone or of document D10 in combination with either documents D11 to D13. Thus, the claimed solution, the use of TNF sequestering or signalling antagonists for the treatment of endometriosis, was not obvious.

Reasons for the decision

Admissibility of the appeal

1. The appellant's grounds of appeal largely consist of verbatim repetitions of arguments that the appellant made before the opposition division. The grounds of appeal integrate these verbatim texts with a new structure for the appeal procedure. However, the fact per se that the points made in the statement of grounds of appeal do not go beyond those made before the opposition division does not automatically make the appeal inadmissible. Whether it is required that new arguments be submitted to render an appeal admissible is strongly dependent on the specific facts and merits of each case. What is decisive for an appeal to be admissible is whether the grounds of appeal can be

considered as a true response to the reasons given by the first instance for their decision. The established case law on this issue (see Case Law of the Boards of Appeal, 5th Edition, VII.D.,7.5.4, page 621) requires that the grounds for appeal should specify the legal and/or factual reasons on which the case for setting aside the decision is based. The arguments must be clearly and concisely presented to enable the board and any other party/parties to understand immediately why the decision under appeal is alleged to be incorrect without first having to make an investigation of their own.

2. As ruled by the board for example in decision T 646/92 of 13 September 1994 this requirement is not seen as fulfilled if there is a mere general reference to the previous submissions in the first instance proceedings, for example as in the case T 646/92 (see *supra*) by simply saying "... for the substantiation of the appeal applicants refer to previous responses filed by the applicants in the prosecution. No further substantiation will follow." Such a bare reference differs from the present case where the appellant has selected three submissions from among its previous arguments and has worked these submissions into a new written structure specifically designed for the appeal.
3. In the present case the decision was to reject the opposition, which implies that the arguments of the opponent did not convince the opposition division and therefore the board understands immediately that now the opponent/appellant tries to persuade the board with the same arguments which did not succeed in the first instance. This does not require the board or the

respondent to make further investigations on their own to understand in which way the decision under appeal is contested by the appellant. The board is therefore convinced that the appeal is admissible.

Amendments (Article 123(2) EPC)

4. The appellant submits that the subject-matter of claim 2 as far as it relates to the improvement of the implantation and fertility rate by reducing endometriotic lesions through the application of TNF sequestering or signalling antagonists alone, i.e. in the absence of active agents other than TNF antagonists, had no basis in the application as filed.

5. However, claims 14 and 17 of the application as filed relate to the "[u]se of a TNF antagonist together with a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition for the treatment and/or prevention of endometriosis-related infertility" and to a "[p]harmaceutical composition containing a TNF antagonist, together with a pharmaceutically acceptable carrier, in the treatment and/or prevention of endometriosis-related infertility". Moreover, it is stated on page 7, lines 21 to 28 of the application as filed: "The invention described herein clearly shows that the unexpected result that sequestering TNF [...] by **means of a TNF antagonist**, reduces endometriotic foci in a rat experimental model. This model also demonstrates [...]. The reduction of endometriotic lesions using TNF antagonists can also improve fertility rates, ..." (emphasis added by the board).

6. The board agrees that the application as filed discloses the use of the TNF antagonists referred to in the claims in combination with a further active agent which is different from such antagonists for the treatment of endometriosis-related infertility. However, in the light of the passages cited above the board is convinced that the skilled person would not give the disclosure of this combination such a weight that the administration of a pharmaceutical composition comprising a sequestering or signalling TNF antagonists as the only effective agent for the treatment of endometriosis-related infertility as a further treatment option would not directly and unambiguously had come to his mind. Therefore, claim 2 fulfils the requirements of Article 123(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

7. The appellant pursues two lines of argument, first that the specific example in the patent does not in fact demonstrate a reduction of endometriotic foci, second that, even if this is accepted for the specifically exemplified compound, the one example was neither sufficient to make it credible that the effect was achieved by all antagonists referred to in claim 1 nor was it sufficient to make credible that the treatment according to claim 2, the improvement in the implantation and fertility rate could be achieved.
8. Regarding the first line of argument the appellant submits that firstly, the results given for the specific antagonist TNF-RI in Table II and Figure 1 could not be properly evaluated because of the lack of data for the control group, the sham-operated rats,

- that, secondly the reported size reduction of endometriotic foci after two days for the TNF-antagonist treated group is not statistically significant and that finally, the effect obtained in a rat model and could not be extrapolated to humans.
9. The assay disclosed in paragraphs [0052] to [0054] aims at determining the antagonizing effects of a soluble TNF receptor, TNF-RI, in a known rat-model of experimental endometriosis. According to paragraph [0048] endometriosis is artificially induced by resecting a fragment of endometrial tissue and transplanting it onto the inner surface of the uterus of the rat. For the "sham-operated" rats an endometrial fragment of the uterus is similarly removed, but a piece of fat is transplanted onto the uterus wall (paragraph [0049]).
 10. In view of the whole experimental set-up, the board considers that the sham-operated group of rats serves as a control group to ensure that endometriosis is not induced by the surgical procedure alone. The statement at the end of paragraph [0054] that "engraftments were not observed in the sham operated animals at any time" supports this view.
 11. The parameter determined in the rat-model assay is the reduction of the size of the engrafted endometriotic foci (paragraph [0052]). The animals are divided in three groups: one is treated with TNF-RI, the second one, which serves as a negative control, with saline solution and the third one, which serves as the positive control, with Antide, a compound known to be effective in the reduction of endometriotic foci.

Measurements were made two and nine days after initiation of the treatment. The results are expressed in Table II and Figure 1, respectively, as the mean percentage inhibition of engrafted endometrium fragments. Since the sham-operated rats have not developed endometriotic foci, this parameter cannot be determined in this group of animals (see citation in point 10 above). Therefore, contrary to the appellant's submission, it would logically and scientifically not be appropriate to include the sham-operated rats in the evaluation of the parameter under consideration, i.e. the reduction of the size of endometriotic lesions, and therefore they cannot possibly serve as a control in an assay for the determination of this parameter.

12. Furthermore, the appellant submits that compared to the original size the percentage of size reduction after two days of 33% in the group treated with the TNF antagonist was not statistically significant as is apparent by a comparison with the saline treated group where a reduction of 19.5% was found after two days. However, in the board's view, it is not appropriate to consider the size reduction after two days in isolation when assessing whether TNF-RI is effective. By also taking into account the values at day nine for the saline and TNF-RI treated animals, it is apparent that the size reduction in the TNF-RI group is considerably more pronounced than in the saline treated group, i.e. 64% versus 25%. The board, when also regarding the size reduction at day nine, considers that the low degree of size reduction at day two in the TNF antagonist treated group, rather than being evidence for the absence of an effect, demonstrates that there is an effect, but that it takes some time to build up.

13. In view of the above conclusion that the data for size reduction is convincing, the respondent's criticism that the actual percentage values of size reduction for the saline group of 19.5% and 25% are neither shown in Figure 1 nor in any other Figure or elsewhere in the patent need not be considered.

14. As to the extrapolation of the results from the rat model to humans, the appellant refers to the declaration by Dr. Cornillie. It is first stated in point 4 of that declaration that the patent "does not provide sufficient evidence that in fact TNF RI would in fact treat endometriosis in human patients, but merely discloses some preliminary data that a rat model shows some reduction in size of endometriotic foci, which would not be predictive of effective treatment of endometriosis in humans ...". Secondly, it is stated in the same declaration in point 5: "In fact even though I have done a more predictive study (2004 ASRM, Philadelphia. Fertil.Steril. 82 (suppl.2) S84, 2004) of a TNF antagonist antibody in baboons and potential positive effects on this endometriosis model was shown, there in fact have been no positive therapeutic effect in humans to date for treating endometriosis. Accordingly, it is my opinion that the data presented for TNF RI in the Opposed Patent is not predictive of a successful human treatment..."

15. It is established case law that for an objection of lack of sufficient disclosure to be able to convince a board it has to be substantiated by verifiable facts (for example decision T 19/90, OJ EPO 1990, 476, point 3.3 of the reasons).

16. However, Dr. Cornillie's first statement mentioned above is not backed up by evidence at all. A possible way of convincing the board of the opinion given in the declaration could have consisted for example in a technical/scientific evaluation as to why the "preliminary data" in the rat model cannot be predictive of effective treatment of endometriosis in humans. The board would like to draw attention to the fact that, according to the case law of the Boards of Appeal and to the granting practice of the EPO, data obtained from animal models are usually accepted as evidence for the sufficiency of disclosure of a claimed human treatment, unless there is convincing evidence, i.e. verifiable facts and evidence in the sense of decision T 19/90 (see point 15 above), that the treatment does not work for human beings. For example, in decision T 219/01 of 15 December 2004 the board denied that the requirement of sufficiency of disclosure was fulfilled with regard to subject-matter directed to a compound for the treatment of AIDS in the light of post-published data from clinical trials showing that no statistically significant effect was attributable to the tested compound (see point 5.2 of the reasons), although the patent reported the successful treatment in a chimpanzee model. In the present case no such evidence is on file and therefore the board finds the present circumstances well within the framework of the established case law. The same answer is applicable to the opinion concerning the lack of a therapeutic effect in humans as expressed in the second statement cited above. Hence, since the necessary evidence is missing that treatment with soluble TNF-RI would not also result in a size

- reduction of endometriotic foci in humans, no case has been made out for an insufficient disclosure in so far.
17. Thus, in the board's judgement, the data in Table II and in Figure 1 demonstrating that the TNF antagonist TNF-RI achieved a significant reduction of the size of endometriotic foci make it plausible that TNF-RI would be useful in the treatment of endometriosis in humans.
18. The appellant further argues that even if it is accepted that the specific antagonist TNF-RI achieves the effect, this single example was not sufficient to make it credible that all antagonists referred to in the claims achieved the same effect. In support of this argument the appellant refers to Dr. Cornillie's declaration stating in point 5 that while TNF antibodies worked in treating **Crohn's disease** another type of TNF antagonist, a TNF-RII receptor fusion protein known under the trademark name "Enbrel" (also known under the name "etanercept"), did not work in treating the same disease. However, in the board's view, the differing activity of two different types of TNF antagonists in the treatment of a disease which, on the basis of the available evidence the board has to consider as being unrelated to endometriosis, is not appropriate to demonstrate that some of the TNF sequestering or signalling antagonists according to claim 1 might not work in the treatment of **endometriosis**.
19. Rather, in the board's view, post-published documents D32 and D33 provide evidence to the contrary in that they disclose that "Enbrel" and the anti-TNF monoclonal antibody c5N reduced endometriosis in baboons, an

animal model which is expected better to mimic the situation in humans than a rat model.

20. The appellant referred to case law to support the argument that the single example of an effective TNF antagonist was not sufficient to prove that each of the antagonists referred to in the claim 1 was effective. The board considers decision T 435/91 (OJ EPO, 1995, 188) to be the most relevant of the cited cases. The subject-matter of the claims under consideration in this decision related to a product. One of its essential constituents, an additive, was defined by functional features and only one example of such additive was given in the patent. The question was whether the skilled person had sufficient information to obtain all alternatives falling under the functional definition. However, these are not the specific circumstances of the present case because, firstly, the claims are directed to a second medical use and secondly, the appellant's argument does not turn on the question whether or not the functional definition of the compounds used, i.e. TNF sequestering or signalling antagonists was so broad that substantially all compounds falling under said definition could not be obtained. It is stated in decision T 435/91 (supra; point 2.2.1, fifth paragraph of the reasons) that "the description with or without the relevant common general knowledge must provide a fully self-sufficient technical concept as to how this result is to be achieved".

21. In the present case the concept underlying the claimed medical use, and which is derivable from the whole description of the patent in suit, is that the

suppression of TNF levels or its effects exerted via the TNF signalling pathway are an effective treatment for endometriosis and the symptoms associated therewith and that this effect is achieved with TNF sequestering or signalling antagonists which are either known or may easily be prepared (paragraph [0028] of the patent in suit). Thus, the reference to the reasoning of the board in case T 435/91 (supra) does not help the appellant's case. In summary, the board is not convinced that the demonstration of only one TNF antagonist was insufficient to make it credible that all antagonists referred to in the claims achieved the claimed effect.

22. As regards the objection of lack of sufficient disclosure of the invention set out in independent claim 2 (see section VI above, third paragraph), the same reasoning as stated above in points 15 to 17 applies also here, as no evidence has been presented to support the argument that the patent does not sufficiently disclose an improvement of fertility. Rather, since it is generally acknowledged that the reduction of endometriotic lesions also improves fertility rates, as the normalization of genital structure has a positive effect on the implantation rate (paragraphs [0008], [0010] and [0023] of the patent and document D22 showing that the embryonic implantation rate is reduced in case of endometriosis), the board considers that the results in Table II and Figure 1 also support a finding of sufficiency of disclosure as regards claim 2.

The requirements of Article 83 EPC are fulfilled.

Novelty (Article 54 EPC)

23. Claim 1 relates to the use of TNF sequestering or signalling antagonists for the treatment of endometriosis. The appellant argues that this definition in fact refers to **any** type of an antagonistic compound in the light of document D1, which defines an "antagonist" in a very general manner as "a substance that tends to nullify the action of another". However, the board remarks that even in the light of document D1 such a broad interpretation of the term "antagonist" is not justified, because the document rather puts emphasis on the notion of complementarities by specifying further immediately after the sentence cited above "as a drug that binds to a cell receptor without eliciting a biological response".

Hence, in the board's opinion, it is a necessary, but not an exhaustive, characterisation of the claimed antagonists that they are a "substance that tends to nullify the action of another".

24. According to the description "sequestering antagonists" are "antagonists that can bind to or sequester the TNF molecule itself with sufficient affinity and specificity to substantially neutralize the TNF epitope responsible for TNF receptor binding" (paragraph [0027]). "TNF signalling antagonists" are defined as antagonists that can inhibit the TNF signalling pathway activated by the cell surface receptor after TNF binding (paragraph [0027]).

It is common general knowledge that the suppression of the function of a protein may occur in ways different from those described above for sequestering and signalling antagonists, for example by abolishing the expression of the gene encoding the protein. For that reason the board does not agree with the appellant's view that the definition of the antagonists in claim 1 would cover any type of a TNF antagonist.

25. The appellant submits that documents D2 and D3 disclosed the use of danazol and pentoxifylline, respectively, for the treatment of endometriosis. The respective documents, and in case of pentoxifylline also documents D8 and D43, further disclosed that danazol and pentoxifylline reduce TNF activity. Therefore both compounds had to be considered as TNF antagonists. However, as explained in points 23 and 24 above, claim 1 refers to specific TNF antagonists. There is no evidence before the board how danazol achieves the TNF suppressive function. Document D2 states on page 49 at the bottom of the second column continued on page 50 that the mechanism of the modulator-effects of, inter alia, danazol on monocyte function is unclear but that it is assumed that they are mediated through monocyte steroid receptors. Thus, on the basis of the available evidence the board cannot conclude that danazol is a compound falling under the definition of antagonists in claim 1. Since novelty of claimed subject-matter can only be denied if that subject-matter clearly and unambiguously derivable from the prior art, document D2 is not novelty destroying for the subject-matter of claim 1.

26. As to pentoxifylline, the appellant refers to the passage on page 1231 of document D8 stating that "pentoxifylline is efficacious in suppressing TNF at the level of both TNF mRNA accumulation and TNF supernatant bioactivity" to support its view that this compound was an antagonist as defined in claim 1. However, document D8 discloses also on page 1234 that pentoxifylline suppresses TNF mRNA production: "In this study we demonstrate that pentoxifylline a methylxanthine, dose-dependently suppressed of LPS-induced TNFT [sic] production at the level of mRNA expression". Also document D43 provides evidence that pentoxifylline acts on the mRNA level (Figure 3). Thus, the reduction of TNF supernatant bioactivity mentioned in the passage referred to by the appellant is the consequence of the suppression of mRNA expression and therefore it is not an antagonist falling under the definition of claim 1 with the consequence that document D3 does not anticipate the subject-matter of claim 1.
27. Document D3 discloses that pentoxifylline was not effective in treating endometriosis related infertility. The respondent argued that also for that reason the document did not destroy the novelty of the subject-matter of claim 1. However, in view of the above finding this argument need not be dealt with.

The subject-matter of claim 1 is novel.

Inventive step (Article 56 EPC)

Closest prior art

28. To assess inventive step, this board, in line with the normal practice of the boards of appeal of the European Patent Office, will apply the "problem and solution approach". This involves as a first step identifying the closest prior art. The closest prior art relates to subject-matter from which the claimed invention could most easily be made by the skilled person and thus provides the strongest basis for a challenge of obviousness. According to the case law this requirement is fulfilled by prior art disclosing subject-matter conceived for the same objective as the claimed invention (Case Law of the Boards of Appeal of the European Patent Office, 5th edition 2006, I.D.3.1).
29. The objective of the present invention is the medical treatment of endometriosis and endometriosis-related infertility.
30. The appellant considered either of documents D2, D3, D4, D5, D6, D7 or D10 and the respondent considered document D2 as the closest prior art document.

Only two of these documents actually disclose a medical treatment of endometriosis, namely documents D2 and D3.

Although the gist of the experiments disclosed in document D2 is that danazol modulates the levels of TNF and IL-1 released by in vitro-cultured activated monocytes, it is stated in the introduction of document D2 that "[d]anazol, an isoxazole derivative of the synthetic steroid 17a-ethinyl testosterone, has been the mainstay of the medical management of endometriosis for over a decade".

Document D3 discloses a clinical trial wherein the effect of pentoxifylline on endometriosis-related infertility was tested. It is stated on page 2049 of the document that this treatment did **not** help fertility.

Hence, the board considers the disclosure in document D2 of the use of the compound danazol for the treatment of endometriosis as the closest prior art.

Problem and solution

31. In view of the hypo-estrogenic and hyper-androgenic effects of danazol (see for example the patent paragraph [0011]) the problem to be solved by the patent is the provision of an alternative medical treatment for the treatment of endometriosis and endometriosis-related infertility and which does not have the mentioned side effects.

The problem is solved by the use of TNF sequestering or signalling antagonists. The patent makes it plausible that the problem is solved (see paragraphs [0056] and [0057] of the patent and point 17 above).

Obviousness

32. The question to be answered is whether or not the skilled person would have been prompted by the teachings in the prior art to replace danazol in the therapy of endometriosis and the related infertility by TNF sequestering or signalling antagonists. The appellant says yes in the light of the disclosures in either of documents D2 to D7 and D10 alone or in view

of a combination of documents D10 with either of documents D11 to D13.

Document D2

33. Document D2 reveals that stimulated monocytes cultured in vitro produce IL-1 β and TNF and that this production is suppressed by danazol. It is mentioned that IL-1 β and TNF are present in peritoneal fluid of some women with and without endometriosis and that danazol may suppress peritoneal macrophage production of IL-1 β and TNF (page 50). It is stated in the abstract of document D2: "These findings suggest possible new mechanisms of action for danazol in the treatment of endometriosis and infertility associated with immune abnormalities". Thus, in the board's view, the skilled person would derive from document D2 an explanation of this action of danazol in the treatment of endometriosis rather than the suggestion to treat endometriosis via a decrease of TNF levels by TNF sequestering or signalling antagonists.

Document D3

34. Document D3 discloses a clinical study assessing the effects of pentoxifylline on the fertility of infertile women with minimal or mild endometriosis. In the course of an enumeration of some of its known activities it is mentioned that pentoxifylline inhibits tumour necrosis factor *in vitro* (page 2049, first column, first paragraph). Moreover it is stated, that it has been suggested that immunomodulation of peritoneal inflammatory cell hyper activation with pentoxifylline may represent a new modality to treat the essential pathophysiology of endometriosis (page 2049, first column, second paragraph). The result of the clinical study presented in document D3 was however: "Therefore there is no evidence from this study that immunomodulation with pentoxifylline aids fertility in those women with minimal or mild endometriosis." (page 2049, first column, in the middle of the third paragraph). Thus, in the board's view rather than being prompted to reduce TNF levels as a treatment option for endometriosis, the skilled person learns from document D3 that pentoxifylline is not suited for treating endometriosis-related infertility.

Document D4

35. Document D4 discloses that an increase of the adhesion of endometrial stromal cells to peritoneal mesothelial cells by TNF was found in an *in vitro* cell adhesion assay. In the board's view, the skilled person might have considered this result *per se* as a promising basis for the development of a treatment for endometriosis by lowering TNF levels since the adherence of endometrial

cells to other cells is certainly one of the necessary events during the development of endometriosis. However, the skilled person would have balanced this result against the authors' careful statements:

"Tumor necrosis factor may play a facilitory role in the development of endometriosis." (Abstract).

"Therefore, it might induce the expression of cell adhesion molecules in mesothelial cells in vivo and play a role in the initiation of endometriosis [...]. This is the subject of a forthcoming investigation." (page 1200, sentence bridging the two columns).

"In view of the complexity of the initiation of the process of endometriosis, in which exfoliated endometrial cells from retrograde menstruation grow onto peritoneal mesothelium in the pelvis, more information is needed on the interaction between normal endometrial or ectopic endometriotic cells and the peritoneal mesothelium, [...]." (page 1200, second column, last paragraph).

Thus, in the board's view, when considering the disclosure of document D4 as a whole, the skilled person would have considered the results in document D4 of such a preliminary nature that they would not have suggested to him/her to treat endometriosis by interfering with the TNF levels alone.

Documents D5 and D6

36. Both documents D5 and D6 report that the level of TNF is increased in the peritoneal fluid of women suffering

from endometriosis. It is noted in document D6 that TNF may have a "key role in controlling cytokine synthesis in the peritoneal environment of endometriosis" (page 596, second column, second paragraph). However, there is no disclosure in either of documents D5 or D6 - or in any other available prior art document - which events actually lead to the increase in the TNF concentration. In fact, it is stated in document D5 that "[t]he question remains as to whether the increase in PF-TNF (note by the board: "PF" is the abbreviation for "peritoneal fluid") levels and incidence associated with endometriosis, [...] is a cause or consequence of these pelvic disorders." And document D6, which is published eight years after document D5 still states that "endometriosis remains an enigma in spite of extensive clinical investigations and experience. The pathogenesis of endometriosis and its link to infertility is controversial". However, in the board's view, knowledge about the mechanism leading to the increase of the TNF concentration would at least be necessary to prompt the skilled person to start thinking about whether the reduction of the amount of TNF, or the effects of TNF, could be an effective treatment. This is because the mere knowledge of the up-regulation of one factor in the framework of a disease is per se not an indication that the down-regulation of that factor could be the basis for a treatment. Thus, the board concludes that neither of document D5 or D6 suggest to treat endometriosis and the related infertility by suppressing the TNF level with TNF sequestering or signalling antagonists.

Document D7

37. The appellant submits that the disclosure in document D7 of the use of TNF-neutralizing IgG antibodies to nullify the effect of TNF rendered the subject-matter of claims 1, 2 and 11 obvious. However, the focus in document D7 is the determination of the levels of IL-8 in peritoneal fluid and whether or not they are modulated by IL-1 and TNF. It is reported that the concentration of IL-8 mRNA is increased after incubation with IL-1 and IL-8 and decreased after treatment with either an anti-IL-1 serum or a TNF neutralizing antibody (Figure 6). The board is convinced that the skilled person would not derive from this use of an anti-TNF antibody the indication that TNF antagonists such as TNF antibodies would be useful in the treatment of endometriosis.

Document D10

38. Document D10 summarizes the state of the art knowledge in 1995 about endometriosis. It is in particular stated that "if endometriosis is believed to be the consequence of immunological derangement, then the treatment has to be directed at correcting immune function." (page 6, second column). By referring to evidence suggesting that immunomodulation could be achieved by non-specific immune modulators (page 6, second column), the authors of document D10 conclude that "prime candidates for consideration as non-specific immunomodulators are some of the drugs utilized by Steinleitner in his animal experiments,..." (page 7). The appellant argues that the skilled person would have understood that this reference refers to compounds such as danazol or pentoxifylline, for example disclosed in documents D2 and D3, respectively,

and which, as argued in the context of the assessment of the novelty of the claimed subject-matter (see points 23 to 26 above) are both TNF antagonists falling under the definition given for these compounds in the claims.

39. However, notwithstanding which compounds are referred to in the above-cited statement, according to document D10 the compounds of choice for the endometriosis treatment are **non-specific** immunomodulators (see the quotation above). TNF sequestering and signalling antagonists are however compounds specifically interacting with one single compound or the pathway it initiates. The board considers that the skilled person would therefore not regard such compounds as "non-specific" immunomodulators. Therefore, the teaching in document D10 would not lead the skilled person in an obvious manner to the claimed invention.

Document D10 in combination with documents D11 to D13

40. The statement on page 7 of document D10 carries on with a further suggestion: "Prime candidates for consideration as non-specific immunomodulators are [...] and also anti-malarials now widely and successfully used in the treatment of autoimmune conditions as rheumatoid arthritis." The appellant argues that this disclosure in combination with the teaching in either of documents D11 to D13 relating to anti-TNF antibodies as an effective treatment for rheumatoid arthritis rendered the claimed subject-matter obvious.
41. Document D11 discloses the generation of anti-TNF antibodies and their use for the treatment of

rheumatoid arthritis. Document D12 discloses the treatment of rheumatoid arthritis with the anti-TNF monoclonal antibody cA2 which is, according to the appellant's submission, the specific antibody tested in document D11 and which is also called infliximab and known under the trademark name Remicade. Document D13 on page 147 under the definition "Remicade" indicates that this compound is useful in combination with another drug to "improve the physical function in patients with active rheumatoid arthritis and severe ankylosing spondylitis. Thus, documents D11 to D13 relate to compounds which specifically interact with one compound, i.e. TNF. The gist of the endometriosis treatment suggested in document D10 is however the use of non-specific immunomodulators (point 39 above). Therefore, in the board's view the skilled person would not have been prompted to a combination of document D10 with either of documents D11 to D13 when looking for an alternative treatment for endometriosis.

42. In summary, no case has been made out that the skilled person would have replaced danazol in the treatment of endometriosis and the related infertility by TNF sequestering or signalling antagonists in an obvious manner. The board therefore concludes that the subject-matter of any of claims 1 or 2 and of the claims dependent thereon fulfils the requirements of Article 56 EPC.

Cancellation of the oral proceedings - Right to be heard

43. Since both parties have requested oral proceedings in case the board was not inclined to decide in their favour, the board has summoned for oral proceedings and thereby observed the fundamental obligation to hear the parties as required by Article 113 (1) EPC. By announcing that it will not attend these oral proceedings, the appellant relies on its written case (Article 15(3) of the Rules of Procedure of the Boards of Appeal). The respondent has withdrawn the request to be heard at oral proceedings insofar as the question of admissibility of the appeal is concerned. Since the board decided in favour of the respondent regarding all remaining issues, it was not necessary to hear the respondent further to observe the right to be heard under Article 113(1) EPC and thus the oral proceedings were cancelled.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chair:

P. Cremona

U. Kinkeldey