

Internal distribution code:

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

D E C I S I O N
of 9 May 2005

Case Number: T 0676/01 - 3.3.04

Application Number: 91920172.3

Publication Number: 0512090

IPC: A61K 38/55

Language of the proceedings: EN

Title of invention:
Treatment of inflammation

Patentee:
Sonoran Desert Chemicals LLC

Opponents:
ZLB Behring GmbH
Genzyme Transgenics Corporation
Bayer AG

Headword:
Treatment of inflammation/SONORAN DESERT CHEMICALS LLC

Relevant legal provisions:
EPC Art. 123(2), 84, 54, 56, 87(4)

Keyword:
"Main request: Right to priority (yes): added subject-matter (no)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
J 0001/92

Catchword:
-



Case Number: T 0676/01 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 9 May 2005

Appellant I: Sonoran Desert Chemicals LLC
(Proprietor of the patent) 4250 N. Drinkwater Blvd., 4th floor
Scottsdale, Arizona 85251 (US)

Representative: Bassett, Richard Simon
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD (GB)

Appellant II: ZLB Behring GmbH
(Opponent 01) Postfach 1230
D-35002 Marburg (DE)

Representative: Lauppe, Hans Friedrich, Dr.
ZLB Behring GmbH
Postfach 12 30
D-35002 Marburg (DE)

Appellant III: Bayer AG
(Opponent 03) Konzernbereich RP
Patente und Lizenzen
D-51368 Leverkusen (DE)

Representative: Chapman, Paul William
Kilburn & Strode
20 Red Lion Street
London WC1R 4PJ (GB)

Other Party: Genzyme Transgenics Corporation
(Opponent 02) Five Mountain Road
Framingham, MA 01701 (US)

Representative: Ruffles, Graham Keith
Marks & Clerk
66-68 Hills Road
Cambridge
Cambridgeshire, CB2 1LA (GB)

Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
8 May 2001 concerning maintenance of European
patent No. 0512090 in amended form.

Composition of the Board:

Chair: U. M. Kinkeldey
Members: R. E. Gramaglia
S. U. Hoffmann
M. R. J. Wieser
G. E. Weiss

Summary of Facts and Submissions

I. European Patent No. 0 512 090 (application No. 91 920 172.3, published as WO-A-92/06706) claiming priority from US 598,241 of 16 October 1990 (document "P1"), US 643,727 of 18 January 1991 (document "P2") and US 683,620 of 11 April 1991 (document "P3") was filed on 26 September 1991. The patent relates to the treatment of inflammation and was granted on the basis of 8 claims, of which claim 1 read as follows:

"1. The use of alpha-1-antitrypsin, secretory leucocyte protease inhibitor, C-reactive protein, serum amyloid A protein and/or alpha-2-macroglobulin, their analogs, salts or derivatives which inhibit the degranulation of mast cells and/or have an affinity to the mediators of mast cells, for the preparation of a pharmaceutical composition for the treatment of diseases implicated by mast cells, neutrophils, T-cells and their mediators."

II. Notices of opposition were filed by opponents (01) to (03) all requesting the revocation of the European patent on the grounds of Article 100(a), (b) and (c) EPC. The opposition division maintained the patent on the basis of the claims of the "New Auxiliary Request 2" then on file.

III. The patentee (appellant I) and opponents 01 and 03 (appellants II and III) filed appeals against the decision of the opposition division.

IV. Two communications were sent, expressing the board's provisional view.

V. Oral proceedings were held on 9 May 2005, during which appellant I filed a new main request (claims 1 to 7 and pages 2 to 8 of the description) and auxiliary requests 1 to 5. Claim 1 of the new main request read as follows:

"1. The use of alpha-1-antitrypsin, secretory leucocyte protease inhibitor, C-reactive protein, serum amyloid A protein and/or alpha-2-macroglobulin, their analogs, salts or derivatives which inhibit the degranulation of mast cells and/or have an affinity to the mediators of mast cells, for the preparation of a pharmaceutical composition for administration to the site of disease or injury, of diseases implicated by mast cells, and their mediators, wherein the disease is asthma or a skin disease, and, if the disease is a skin disease, then only a single serine protease inhibitor is present in the composition."

Claims 2 to 7 related to specific embodiments of the use of claim 1.

VI. In the present decision, the following abbreviations are used: AAT = alpha-1-antitrypsin (also termed α_1 -AT or α_1 -PI); ACT = alpha-1-antichymotrypsin.

VII. The following documents are cited in the present decision:

E1 Hubbard R. C. et al., Ann. Int. Med.,
Vol. 111, No. 3, pages 206-212 (1989);

E2 EP-A-0 289 336;

- E4 Gadek J. E. et al., The American Journal of Medicine, Vol. 84 (Suppl. 6A), pages 1-90 (1988);
- E7 EP-A-0 432 117;
- E15 JP-A-1-283217 (English translation);
- E21 US-A-5,008,242;
- E23 Larsen G. L. et al., Ann. Rev. Immunol., Vol. 1, pages 335-359 (1983);
- E24 Zweiman B. et al., Clinical Research, Vol. 36, No. 3, page 257A (1988);
- E26 Schechter N. M. et al., J. Biol. Chem., Vol. 264, No. 35, pages 21308-21315 (1989);
- E27 Wasserman S. I., Annals of Allergy, Vol. 63, pages 546-548 (1989);
- E39 Pina J. S. et al., Postgraduate Medicine, Vol. 101, No. 4, pages 153-156 (1997);
- E64 Harrison's Principles of Internal Medicine, page 303 (1994);
- E60 Forteza R. et al., Am. J. Crit. Care Med., Vol. 154, page 36-42 (1996);
- E65 Wachter A. M. et al., Annals of Allergy, Vol. 69, pages 407-412 (November 1992);

- E77 Breit S. N. et al., Clinical Immunology and Immunopathology, Vol. 35, page 363-380 (1985);
- E78 Kaliner M., J. Allergy Clin. Immunol., Vol. 83, No. 2, Part 2, pages 510-520 (February 1989);
- E79 Ishizaka T. et al., Fed. Proc., Vol. 43, No. 13, pages 2840-2845 (1984);
- E80 English translation of Urata C. et al, Nihon Kyobu Shikkan Gakkai Zasshi, Vol. 23, No. 6, pages 660-665 (June 1985);
- E81 Beckman G. et al, Acta Dermatovener. (Stockholm), Vol. 60, pages 163-164 (1980);
- E82 Barszcz D. et al., Arch. Dermatol. Res., Vol. 280, pages 198-206 (1988);
- E83 Heng M. C. Y. et al., British Journal of Dermatology, Vol. 112, pages 129-133 (1985);
- B4 Rest R.F., Methods in Enzymology, Vol. 163, pages 309-326 (1988);
- B6 English translation of Glukhenky B. T. et al., Vestnik Dermatologii i Venerologii, Vol. 1, pages 53-56 (1985).

VIII. The submissions by appellant I (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Chapman appeal

- By letter dated 5 July 2001, Mr Chapman filed a Notice of Appeal. The letter failed to identify an appellant other than Mr Chapman himself, who was not himself a party to the proceedings, nor was any address of an appellant indicated. Therefore, the appeal had to be rejected as being inadmissible (cf. decision J 0001/92 of 15 July 1992 and the Case Law of the Boards of Appeal, 4th Edition, English version, page 522, paragraph VII.D.7.3.1).

Article 123(2) EPC

- The wording in claim 1 "if the disease is a skin disease, then only a single serine protease inhibitor is present in the composition" was a positive feature which restricted the scope of claim 1 and should not be seen as a disclaimer. In any case it was based on the application as filed and did not add subject-matter. A basis therefor could be found in claim 14 as filed relating to one serine protease; in Example II on page 12, last paragraph, wherein the use of AAT as the sole active principle was clearly presented as an alternative to the use of a combination of AAT and ACT; in page 11, first full paragraph ("alone"); in page 4, line 29 ("alone or in combination"); and in page 8, last sentence, wherein the "preferable" use of ACT with the AAT showed that it was optional.

Article 84 EPC

- The medical use of claim 1 was sufficiently delimited over known medical uses involving AAT-deficient patients.

Priority Rights (Article 87(4) EPC)

- Claim 1 had multiple priorities. Insofar as it related to asthma it enjoyed the filing date of the international patent application (26 September 1991). Insofar as it related to inflammatory skin diseases, it enjoyed the filing date of priority document P2 (18 January 1991).
- A claim defined the invention. If priority rights might be lost by changing the subject-matter of a claim, the same had to apply when rights were preserved upon amendment of a claim in order to avoid an already claimed subject-matter.
- There was no legal basis for asserting that a disclaimer could not simultaneously restrict a claim to subject matter that was novel and entitled to a given priority date. Nor was there any legal basis for asserting that one had first to assess entitlement to priority (under Article 87(4)) and then assess the effect of the prior art.
- There was no legal basis for saying that a disclaimer could not be used to validate a priority claim.

Novelty

- Document E2 was concerned with the aerosolization of therapeutic proteins and in particular with AAT for treating emphysema by inhibiting elastase.

- Document E7 disclosed AAT as being the "other serine protease inhibitor" to be used together with ACT. There was no disclosure of AAT alone, so that the wording in claim 1 "if the disease is a skin disease, then only a single serine protease inhibitor is present in the composition" was effective in excluding the disclosure of document E7.

- Claim 1 of this request was drafted as referring to a second/further medical use, the diseases to be treated being inter alia skin diseases implicated by mast cells and their mediators. Document E15 disclosed the use of AAT or α 2-macroglobulin and topical creams containing them in the treatment of inflammatory skin diseases. However, the inflammatory proteases to be inhibited were SH-proteases to be found in the digestive tract, not those of mast cells, which were fixed in tissues and differed from the serine proteases of the invention. There was also no indication that the disease in document E15 was implicated by mast cells, as required by claim 1.

- There were different sources of inflammation, not necessarily provoked by mast-cells.

Inventive step

Asthma

- Document E2 told that elastase had to be inhibited with AAT in order to protect against inflammation, while document E27, relating to mast cell-mediated inflammation, did not mention elastase. Hence, the skilled person would not combine these documents.

- Document E16 was concerned with the production of recombinant AAT, coupled with a list of diseases to be treated, wherein asthma was not mentioned. There were no biological data and no suggestion encouraging the person skilled in using AAT to treat asthma.

- It did not make sense to treat AAT-deficient asthma at the site of the disease, since the skilled person would aim at re-establishing the protease/anti-protease balance in blood by iv (intravenous) injections.

- Document E77 related to the treatment of congenital AAT-deficiencies. There was no mention of asthma, but merely a suggestion that a link could exist between a genetic deficiency of AAT and asthma. According to document E77, severe AAT deficiency was linked to emphysema, whereas only a mild degree of AAT deficiency was linked to asthma. It was only this severe AAT deficiency that could be treated with AAT in a replacement therapy by iv injections. Document E4 confirmed this current dogma. Moreover, it did not make sense to treat

this genetic deficiency of AAT in blood at the site of the disease.

- There were two kinds of asthma: mast cell-dependent asthma (this was claimed) and steroid-dependent (not claimed), as shown by post published document E39, taken as expert opinion.

- Document E78 showed the whole picture at that time: there was a plethora of possible causes/cells/mediators involved in the inflammation associated with asthma, among which only two proteases, namely tryptase and chymotryptic proteinase (Table II). However, these proteases were not inhibited by AAT. Document E78 did not formulate any treatment for asthma.

- The authors of E80 reported that severe attacks of bronchial asthma were associated with raised levels of AAT in the blood, a finding that did not suggest that externally supplying AAT was going to help. Moreover, it could not be taken for granted that an agent that inhibited histamine release would obviously be useful in the treatment of asthma, since standard antihistamine medicaments were not effective for treating asthma.

- Even if document E7 were part of the state of the art under Article 52(4) EPC for the part of the claims relating to asthma, there was no suggestion in this document to treat asthma with AAT.

Skin Diseases

- As far as the treatment of a skin disease is concerned, document E7 was part of state of the art under Article 54(3) EPC only and so it could not be used to show a lack of inventive step.

IX. The submissions by appellants II and III (opponents 01 and 03), insofar as they are relevant to the present decision, can be summarized as follows:

Chapman appeal

- The appeal was filed in the name of opponent 03, as was clearly indicated in the letter of 5 June 2001, which was signed "CHAPMAN, Paul William Authorised Representative".

Article 123(2) EPC

- No basis could be found in the application as filed for the treatment of a skin disease with a single serine protease inhibitor. There was a basis only for AAT to be used alone.
- The expression "a single protease inhibitor is present" in claim 1 was broader than the list of protease inhibitors of claim 1 (alpha-1-antitrypsin, secretory leucocyte protease inhibitor, C-reactive protein, serum amyloid A protein and/or alpha-2-macroglobulin).
- The expression "to the site" in present claim 1 found no basis in the application as filed,

especially when taken in combination with the treatment of asthma.

- The disclaimer excluded more than it was necessary, as document E7 merely dealt with binary composition comprising AAT and ACT.
- Document E7 was available as prior art under Article 54(2) EPC. Thus, the inclusion of the disclaimer "if the disease is a skin disease, then a single serine protease inhibitor is present in the composition" in claim 1 was not allowable under Article 123(2) EPC.
- A consequence of the "disclaimer" in claim 1 being not allowable under Article 123(2) EPC was that document E7 switched from a status of a document under Article 54(3) EPC to that of a document pursuant to Article 54(2) EPC, depending on whether Article 87(4) EPC was applied ante or post.

Article 84 EPC

- The medical use of claim 1 was not sufficiently delimited over known medical uses involving AAT-deficient patients.

Priority rights (Article 87(4) EPC)

- The treatment of a skin disease with a single serine protease inhibitor could not be directly and unambiguously derived from priority document P2.

- Document E21 represented an earlier filing of the same invention and thus none of priority documents P1 to P3 was the first application for this invention, since the first application US 445005 had not been withdrawn, abandoned or refused, leaving no right outstanding (the corresponding US patent, namely document E21, had been granted). As a consequence of this loss of priority rights, document E7 was a document under Article 54(2) EPC, with the further consequence that the disclaimer introduced in claim 1 for excluding the disclosure of document E7 infringed Article 123(2) EPC.

Novelty

- Document E2 disclosed the use of AAT for treating asthma.
- Document E7 related to the use of ACT in the treatment of inflammatory skin conditions. At page 3, lines 27-28, it was made clear that AAT was preferably combined with ACT. Thus, this document clearly disclosed the use of AAT in the preparation of a medicament to treat skin inflammatory conditions.
- Document E15 disclosed the use of AAT or α 2-macroglobulin and topical creams containing them in the treatment of inflammatory skin diseases caused, inter alia, by bacterial infections, possibly involving mast cells.
- The feature in claim 1 that the skin diseases should be implicated by mast cells and their

mediators was a mere explanation of how the protease inhibitors listed in claim 1 healed said skin diseases.

Inventive step

Asthma

- The closest prior art was represented by document E2 or E16. Both documents related to AAT and its therapeutic uses. Document E2 discussed the use of AAT for treating emphysema, a pulmonary inflammation. Document E16 suggested a list of diseases to be treated with AAT, included chronic obstructive pulmonary disease. Departing from document E2 or E16 it was prima facie obvious that AAT was useful in treating inflammatory conditions in general and to move to the treatment of another pulmonary inflammation condition, asthma, using AAT.
- The subject-matter of claim 1 lacked an inventive step in view of the combination of documents E2 or E16 with one or more of documents E77, E27, E78, E79 and E80.
- Document E77 taught that AAT insufficiency (e.g. congenital insufficiency) contributed to the aetiology of inflammatory conditions, including asthma.
- Document E27 disclosed the role of mast cells and their mediators in the inflammation associated with asthma.

- Document E78 taught the skilled person that IgE-mediated mast cell degranulation was a critical factor in the pathogenesis of asthma, as further shown by document E79, demonstrating that in human lung mast cells, activation by IgE induced Ca^{++} uptake and release of histamine (degranulation).

- Document E80 taught the skilled person that local addition of AAT to IgE stimulated human mast cells inhibited histamine release (degranulation) in a dose-dependent manner and that the authors of this paper concluded that in inflammatory conditions, such as bronchial asthma, AAT controlled histamine release from stimulated human mast cells. Therefore, the skilled person, when considering the closest prior art, i.e. documents E2 or E16, would inevitably proceed to utilise AAT in the treatment of asthma, with the expectation of success.

Skin Diseases

- Insofar as claim 1 related to skin diseases, the claim lacked an inventive step in view of documents E81, E82 and E83. Document E81 disclosed that there was a link between AAT deficiency and the manifestation of an inflammatory skin disease, namely psoriasis. This was confirmed in document E82, disclosing that AAT deficiency was associated with psoriasis and increased AAT activity was a characteristic of symptom-free psoriasis. Document E82 also disclosed that neutrophils and elastase were the main group of cells/mediators involved in psoriasis. Document E82 again confirmed the link

between AAT deficiency and psoriasis and also showed that there was increased proteolytic activity in psoriatic skin and certain of these proteases are indeed inhibited by AAT. Document E83 established that decreased elastase activity correlated with an improvement in psoriasis.

X. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

- claims 1 to 7 of the main request, or in the alternative
- claims 1 to 7 of one of the auxiliary requests 1 to 5

all filed during the oral proceedings.

Appellants II and III (opponents 01 and 03) requested that the decision under appeal be set aside and that the European patent No. 0 512 090 be revoked.

Reasons for the Decision

The "Chapman appeal"

1. Referring to decision J 0001/92 (supra) appellant I maintains that the appeal lodged on 5 July 2001 had been made in the name of the representative, Mr Chapman, rather than in the name opponent 03, and thus it had to be rejected as being inadmissible. However, the board holds the view that this notice of appeal was filed in

the name and on behalf of opponent 03 because Mr Chapman signed the notice as authorised representative (c.f. "Chapman Paul William, Authorized Representative") and the heading to his letter referred to opponent 03 (c.f. "Opposition Thereto by Bayer"), whom he already represented during the opposition proceedings. The present appeal language thus differs from that dealt with in decision J 0001/92 (supra), including a statement (see Section IV) "I, (followed by the name of the representative and his address) file herewith an appeal against the decision of EPO dated September 18, 1991. The appeal is lodged in my own name...". Therefore the board judges that the appeal filed on 5 July 2001 has been made in the name of opponent 03 and is admissible.

Main Request

Article 123(2) EPC

2. Claim 1 relates to a medical use, namely the topical treatment of skin diseases or asthma implicated by mast cells and their mediators by means of serine protease inhibitors. Insofar as claim 1 relates to the treatment of asthma, a basis can be found in the WO application on page 10, line 5, in Example VIII, taken in combination with claim 10.
3. Insofar as claim 1 relates to the treatment of skin diseases, this medical use can be derived from the combination of claims 1, 2 and 3, all of the published WO application.
4. A critical issue has been the question of whether or not the wording in claim 1 "if the disease is a skin

- disease, then a single serine protease inhibitor is present in the composition" can be derived directly and unambiguously from the application as filed.
5. Appellants II and III maintain that no basis can be found in the application as filed for the treatment of a skin disease with a single serine protease inhibitor. However, already the combination of claims 1, 2 and 3 of the WO application provides a basis, but in any case, the expression "when topically applied, a serine protease inhibitor such as...is useful in the treatment of...inflammatory skin diseases" (see page 9, penultimate paragraph) provides an explicit basis for the above wording in present claim 1, i.e., for the treatment of a skin disease with a single serine protease inhibitor. A further basis can be found in claim 14 as filed relating to "at least one serine protease inhibitor"; in Example II on page 12, last paragraph, wherein the use of AAT as the sole active principle is clearly presented as an alternative to the use of a combination of AAT and ACT; in page 11, first full paragraph ("alone or in combination"); in page 4, line 29 ("alone or in combination") and in page 8, last sentence, wherein the "preferable" use of ACT with the AAT shows that it is optional, in the sense that AAT can also be used alone.
6. Appellants II and III argue that the expression "a single protease inhibitor is present" in claim 1 is broader than the list of protease inhibitors of said claim (alpha-1-antitrypsin, secretory leucocyte protease inhibitor, C-reactive protein, serum amyloid A protein and/or alpha-2-macroglobulin). However, owing to the wording of the claim, "a single protease

inhibitor" must of necessity be selected from the list of the above five protease inhibitors. Therefore, the wording "a single protease inhibitor" cannot go beyond this list, although there is a basis for serine proteinase inhibitors in general in claim 1, in page 9, penultimate paragraph and in page 11, last paragraph of the WO application.

7. As for the contention by appellants II and III that the application as filed provides a basis only for AAT to be used alone in skin diseases, the combination of claims 1, 2 and 3 of the WO application provides a basis for any protease inhibitor used alone in the treatment of a skin disease.
8. Appellants II and III question the expression "to the site" in present claim 1 as finding no basis in the application as filed, especially when taken in combination with the treatment of asthma. However this expression finds a basis on page 7, lines 3-4 ("when administered to the site of inflammation") and in claim 1 of the WO application. Administration by inhalation (see ibidem, page 10, first paragraph) is an administration to the site of inflammation of an asthmatic patient.
9. It is argued by appellants II and III that the "disclaimer" excluded more than it was necessary, as document E7 merely dealt with binary composition comprising AAT and ACT. However, the board does not view the wording "if the disease is a skin disease, then a single serine protease inhibitor is present in the composition" as a "disclaimer", but merely as a limitation to one of the many embodiments covered by

- claim 1, which embodiment is expressed as a positive correlation that a single protease inhibitor is used for the treatment of skin diseases. The relevant question is whether there is a basis in the application as filed for the embodiment "single protease inhibitor for the treatment of skin diseases" (the answer is in the affirmative, see points 5 and 6 supra), not whether it excludes more or less than not (or no longer) relevant documents.
10. Since document E7 is prior art under Article 54(3) EPC (see point 21 infra), the contention by appellants II and III that the "disclaimer" in claim 1 is not allowable under Article 123(2) EPC in view of document E7 being full prior art under Article 54(2) EPC, must fail.
 11. Finally, appellants II and III argued that a consequence of the "disclaimer" in claim 1 being not allowable under Article 123(2) EPC was that document E7 switches from a status of a document under 54(3) EPC to that of a document pursuant to 54(2) EPC, depending on whether Article 87(4) EPC is applied ante or post. However, since the embodiment that a single protease inhibitor should be used for the treatment of skin diseases finds a basis in the application as filed, this issue needs not be dealt with further.
 12. In conclusion, the subject-matter of claim 1 and dependent claims satisfies the requirements of Article 123(2) EPC.

Article 84 EPC

13. The only objection raised by appellants II and III under this Article is that the medical use of claim 1 in its present wording is not sufficiently delimited over known medical uses involving AAT-deficient patients. However, to the board this issue is more adequately dealt with in the context of novelty and inventive step (see points 21 onwards).

Priority rights (Article 87(4) EPC)

14. Insofar as claim 1 at issue relates to the treatment of asthma, the parties and the board agree that this subject-matter cannot validly claim any of the priorities and thus the relevant date for establishing the prior art is the filing date of patent application.
15. Insofar as claim 1 at issue relates to the treatment of skin diseases, the topical treatment of skin diseases implicated by mast cells and their mediators by means of serine protease inhibitors is disclosed on page 5, lines 3-5 from the bottom, on page 8, second paragraph in combination with page 9, third paragraph and claim 1 of priority document P2, and illustrated by Examples I, II, III and IV of priority document P2. The five protease inhibitors referred to in claim 1 are listed on page 6, last paragraph of priority document P2.
16. A critical issue is the question of whether or not the wording in claim 1 "if the disease is a skin disease, then a single serine protease inhibitor is present in the composition", i.e., the treatment of a skin disease

- with a single serine protease inhibitor can be directly and unambiguously derived from priority document P2.
17. The above wording finds a basis in priority document P2 as follows: Claim 1: "at least one human serine protease"; Example II on page 11, wherein the use of AAT as the sole active principle is clearly presented as an alternative to the use of a combination of AAT and ACT; page 9, line 7 from the bottom and third paragraph: "alone or in combination"; page 8, third full paragraph: AAT is "preferably used in combination with the ACT" (it is optional to use it alone or in combination); and page 5, line 1: "alone or in combination". The wording on page 6, second paragraph "when topically applied, a serine protease inhibitor such as...is useful in the treatment of...inflammatory skin diseases" provides a further explicit basis for the treatment of a skin disease with a single serine protease inhibitor, according to the above wording in present claim 1.
18. Appellants II and III argue that document E21 represents an earlier filing of the same invention and that thus none of priority documents P1 to P3 is the first application for this invention, since the first application US 445005 had not been withdrawn, abandoned or refused leaving no right outstanding (the corresponding US patent, namely document E21, has been granted). As a consequence of this loss of priority rights, document E7 switches from a status of a document under Article 54(3) EPC to a document pursuant to Article 54(2) EPC, with the further consequence that the disclaimer introduced in claim 1 for excluding the disclosure of document E7 infringes Article 123(2) EPC.

19. However, document E21 (and application US 445005) discloses ACT-containing compositions for treating skin diseases by inhibition of mast cell chymase (see column 2, lines 46-51). But ACT is not among the list of serine protease inhibitors in present claim 1. The document also does not disclose AAT of its own nor any serine protease inhibitor (other than ACT) alone. In column 6, lines 23-26, it is merely stated that AAT may be used together with ACT. However, the wording in claim 1 at issue "if the disease is a skin disease, then only a single serine protease inhibitor is present in the composition" is effective in excluding the disclosure of E21.
20. In conclusion, since the claimed subject-matter can be found neither in document E21 nor in the priority document underlying it (US 445005), the subject-matter of claim 1, insofar as it relates to skin disease, can validly rely on the filing date of priority document P2 (18 January 1991) for the purpose of establishing the state of the art.

Novelty

Document E7

21. As far as the treatment of skin diseases is concerned, document (E7) is thus part of the state of the art under Article 54(3) EPC. It discloses ACT-containing compositions for treating skin diseases by inhibition of mast cell chymase (see page 3, lines 7-9). But ACT is not among the list of serine protease inhibitors in present claim 1. It does not disclose AAT of its own nor any serine protease inhibitor other than ACT alone.

On page 3, lines 27-28 and page 5, lines 49-50, it is stated that AAT may be the "other serine protease inhibitor" to be used together with ACT. However, the wording in claim 1 at issue "if the disease is a skin disease, then only a single serine protease inhibitor is present in the composition" is effective in excluding the disclosure of E7. The claim is therefore novel over document E7.

Document E15

22. Claim 1 of this request is drafted as referring to a second/further medical use, the diseases to be treated being skin diseases implicated by mast cells and their mediators, while the active principle is one serine protease inhibitor selected from alpha-1-antitrypsin, secretory leucocyte protease inhibitor, C-reactive protein, serum amyloid A protein or alpha-2-macroglobulin.
23. Document E15 discloses the use of AAT or alpha-2-macroglobulin and topical creams containing them in the treatment of inflammatory skin diseases. The relevant issue to be decided is thus whether or not the medical use according to claim 1 represents a distinct (further) medical use vis-à-vis the therapeutic use disclosed in document E15.
24. The skin disease dealt with in document E15 is e.g., periproctitis (see page 3, line 4 from the bottom of the translation) and the proteases to be inhibited are SH-proteases (ibidem, page 2, third paragraph) of plasma or the digestive tract (ibidem, page 1, lines 43-44). These mediators to be inhibited thus differ

- from the serine protease present in mast cells (see claim 1) fixed in tissues, from which the associated proteases and other mediators are not released into the serum/plasma.
25. Furthermore, there are a great many aetiologies of inflammation, not necessarily mast-cell-mediated, each of which identifies a different clinical situation/disease and hence a new sub-group of subjects being treated, e.g., histamine-induced inflammation (see document E80), neutrophil-mediated inflammation (see document E24), leukocyte protease-mediated inflammation (see document B4, page 309, introduction), neutrophil serine collagenase-mediated inflammation (ibidem, page 318) and inflammation of the fat (panniculitis) (see document E64, page 303, bottom of r-h column). Finally, post-published document E65, taken as expert opinion, illustrates in Fig. 4, page 412, other possible mechanisms of inflammation involving T-cells, neutrophils and their mediators. Document E23 lists on pages 342-343 representative mediators of inflammation.
26. Appellants II and III argue that the inflammatory skin diseases dealt with in document E15 are caused by bacterial infections (see page 3, under "Working/Effect"), possibly involving mast cells. However, it can neither be derived from document E15, nor is there any evidence before the board that skin inflammation caused by bacterial infections is mast-cell-mediated, as is required by claim 1 at issue. In any case, eczema and psoriasis (see present claim 5) and atopic dermatitis (see document E65) falling under the category of such mast-cell-mediated skin diseases

are distinct from periproctitis caused by bacterial infections.

27. In view of the foregoing, the board concludes that the feature in claim 1 that the skin disease should be implicated by mast cells and their mediators identifies a new clinical/pathophysiological situation vis-à-vis the SH-protease-mediated skin diseases disclosed in document E15. The above technical feature is not a mere explanation of how the protease inhibitors listed in claim 1 heal the skin diseases since it identifies a new pattern of skin inflammations having mast cells and their mediators as common denominator, and it is only when the skin disease results in the involvement of said mast cells and their mediators that AAT exerts a beneficial role. Therefore, the medical use according to claim 1 represents a distinct (further) medical use vis-à-vis the therapeutic use disclosed in document E15.

Document E2

28. Appellant II and III maintain that the treatment of asthma with AAT is disclosed in a novelty-destroying manner in document E2. However, this document discloses AAT for treating emphysema (see column 2, line 48) by inhibiting elastase (see column 4, bottom). It is true that the document refers to asthma (see column 3, line 9), however, this occurs in the context of the diseases (see column 3, lines 9-11: "...asthma, adult or infant respiratory distress syndrome, emphysema, lung cancer, etc") which can be treated with high mw proteins such as interferons, immunoglobulins, lipocortin, etc, as set out at column 3, lines 2-5. Therefore, the conclusion cannot be drawn that document

E2 discloses the specific combination "AAT" for treating "asthma", let alone asthma implicated by mast cells and their mediators, as required by claim 1 at issue.

29. In conclusion, the subject-matter of claim 1 and dependent claims satisfies the requirements of Article 54 EPC.

Inventive step

Asthma

Closest prior art and problem to be solved

30. Appellants II and III depart from document E2 or E16 as closest prior art. Both documents relate to AAT and its known therapeutic uses. Document E2 discusses the use of AAT for treating emphysema, a pulmonary inflammation (see column 2, lines 25-29 and column 4, lines 62-65) by inhibition of elastase (column 2, line 46). Document E16 suggests a list of diseases related to AAT-deficiency to be treated with AAT, including chronic obstructive pulmonary disease (see page 7, line 29 to page 8, line 11). The problem to be solved starting from either documents, according to all appellants, is the provision of a further and distinct medical use of AAT, namely the treatment of asthma implicated by mast cells and their mediators by administration of the medicament to the site of the disease (see point 27 *supra*).

31. It is argued by appellants II and III that departing from document E2 or E16, teaching that AAT was useful in treating inflammatory conditions in general, it was

obvious to move to the treatment of another pulmonary inflammation condition, asthma, using AAT.

32. However, the current dogma before the filing date of the patent in suit was that severe AAT genetic deficiency was linked to emphysema, whereas only a mild degree of AAT genetic deficiency was linked to asthma (see document E77, under "Introduction"). It was only this severe AAT deficiency which could be treated with AAT in a replacement therapy by iv injections. This dogma finds further support in document E4 (see page 2, column 2, second paragraph), stating that "a strong consensus emerged from all conference participants for recommending that replacement therapy be reserved for only those persons with severe, inherited deficiency of alpha-1-antitrypsin".
33. Therefore, in the board's judgement, the skilled person had prima facie no reasons to use AAT replacement therapy in the mild genetic deficiency associated with some form of asthma, in breach of the current dogma at that time.
34. Moreover, it did not seem to make sense to treat the above genetic deficiency of AAT at the site of the disease, since the skilled person would aim at re-establishing the protease/anti-protease balance in blood by iv injections.
35. As regards the inflammation conditions underlying emphysema, which appellants II and III argue to be common to any inflammatory conditions, including asthma (hence a similar treatment for both diseases), the following should be noted. Firstly, it has already been

emphasized under point 25 supra that inflammation is merely a symptom of a great many different underlying pathophysiologic events and/or biochemical mechanisms, each of which identifies a different clinical situation/disease, the successful treatment of which requires an understanding of these pathophysiologic events (see e.g., document E78, page 519, r-h column, last paragraph). Secondly, the skilled person is taught by documents E2 and E16 that the biochemical mechanism underlying the healing the emphysema-associated inflammation is the inhibition of elastase (document E2) and that the inflammation (if any) accompanying the chronic obstructive pulmonary disease, caused by AAT-deficiency could be healed by re-establishing the protease/anti-protease balance in blood by iv injections of AAT (document E16), i.e., two mechanisms of action very remote from healing mast cell-mediated asthma by switching off the inflammation cascade produced by mast-cells and their mediators with AAT applied topically at the site of the disease (see claim 1). Therefore, the board must conclude that the skilled person departing from this prior art alone had no reasonable expectation of success in treating mast cell-mediated asthma with the same medicament (AAT) used for treating other inflammatory diseases such as emphysema.

36. In conclusion, the argument by appellant II and III that the use of AAT to treat an inflammatory disease such as emphysema, disclosed by documents E2 and E16, rendered obvious to the skilled person to use AAT to treat mast cell-mediated asthma, is not convincing.

37. Appellants II and III further argue lack of inventive step of the subject-matter of claim 1 in view of the combination of documents E2 or E16 with one or more of documents E77, E27, E78, E79 and E80.
38. As for the combination of document E2 or E16 with document E77, the asthma patients referred to in the latter document suffer from a genetic deficiency of AAT (see page 363, under "Introduction"). Therefore, the conclusion arrived at by the board under points 33 and 34 supra also apply to document E77, namely that the skilled person would not use AAT replacement therapy in the mild genetic deficiency associated with this form of asthma, in breach of the current dogma (and there is no suggestion either in document E77 to treat asthma caused by AAT-deficiency with AAT), and that administration of AAT to the site of the disease is not contemplated.
39. Moreover, although the aetiology of asthma is not fundamentally linked to a genetic deficiency of AAT, the above AAT-deficient asthma patients represent 1-2 % of all asthma patients (see post published document E39 cited as expert opinion, page 156, l-h column, last paragraph). These AAT-deficient patients have a predisposition to have asthma (c.f. the expression "hyperactive airways" on page 365, line 5 of document E77) and tend to have a more severe disease characterized by a less response to steroids, which is the medicament of choice (see document E4, page 365, lines 1-7 and document E39, r-h column, last paragraph). Appellant I has cited post published document E39 as expert opinion for showing that asthma in AAT-deficient patients is a disease different from that referred to

in claim 1 at issue since the former does not involve mast cells (see page 155, Fig. 1), and it is treated with steroids. The board agrees that asthma linked to a genetic deficiency of AAT is a pathological situation distinct from the disease to be treated according to claim 1 at issue, namely asthma implicated by mast cells and their mediators. Therefore, in the board's judgement, even if the skilled person departing from document E2 or E16 taken in combination with document E77, decided nevertheless to treat the AAT-deficient asthma patients dealt with in document E77 by application of AAT to the site of the disease (which is not the view taken by the board), he/she would not arrive at the distinct medical use stated in claim 1.

40. As regards the combination of document E2 or E16 with document E27, the latter represents a summary of the knowledge at that time about the role of mast cell-mediated inflammation in asthma (see the title). It can be derived from this document that the biology of mast cells and their mediators was very complex (see page 546, middle column, first full) and that the role of mast cells and their mediators in asthma was not understood (see page 547, l-h column, second full paragraph; page 548 central column, under the heading "Enzymatic Mediators": "...The function of these enzymes in the disease is uncertain"). Moreover, it is stated on page 548, r-h column that tryptase is not inhibited by circulating plasma antiproteases. Therefore, the skilled person departing from documents E2 or E16 and coming across document E77 would not arrive at the medical use of claim 1, relying on the blockage of the inflammation cascade produced by mast-

- cells and their mediators with AAT applied topically at the site of the disease.
41. Furthermore, document E2 (see column 2, line 46 and column 4, bottom) taught that AAT had to inhibit elastase (produced by neutrophils; see patent in suit, page 2, line 41), in order to protect against inflammation, while document E27 relating to mast cell-mediated inflammation did not mention elastase. Hence, the skilled person would not combine these documents.
 42. Appellants II and III rely on document E26 (see page 21308, last full paragraph) for maintaining that the mechanism regulating neutrophil serine proteases such as elastase is the same as that regulating mast cell serine proteases. However, the authors of document E26 merely say that these two mechanisms "may" be the same in the context of "host defence", not inflammation, without providing any proof. Therefore, this unproven hypothesis would further increase the skilled person's uncertainty.
 43. As for the combination of document E2 or E16 with document E78/E79, appellants II and III argue that document E78 taught the skilled person that IgE-mediated mast cell degranulation was a critical factor in the pathogenesis of asthma, as further shown by document E79, demonstrating that in human lung mast cells, activation by IgE-induced Ca^{++} uptake and release of histamine (degranulation).
 44. However, IgE is merely presented in document E78 as one of the many possible factors that can cause mast cell degranulation (see Fig. 1). Moreover document E78 lists

all the possible mediators (see Table III) and mast cell mediators (Table II) involved in asthma, or causes of asthma (Table I). Even if the skilled person turned by "lucky guess" to tryptase or chymotryptic proteinase (Table II), the only proteases among this plethora of potential targets (AAT is not mentioned), the skilled person is taught by document E27 (see page 548, r-h column) that these proteases might not be inhibited by circulating plasma antiproteases and hence by AAT. Given the above uncertainty as to the pathophysiologic events underlying asthma, the author of document D78 refrains from proposing any possible treatment for asthma, let alone an AAT-based treatment (see page 519, r-h column, last paragraph). In conclusion, the combination of document E2 or E16 with documents E78 and/or D79 does not render obvious the medical use of claim 1, relying on the blockage of the inflammation cascade produced by mast-cells and their mediators with AAT applied topically at the site of the disease.

45. As for document E80, appellants II and III maintain that this document taught the skilled person that local addition of AAT to IgE-stimulated human mast cells inhibited histamine release (degranulation) in a dose-dependent manner and that the authors of this paper concluded that in inflammatory conditions, such as bronchial asthma, AAT controlled histamine release from stimulated human mast cells. Therefore, the skilled person, when considering the closest prior art, i.e. documents E2 or E16, would inevitably proceed to utilise AAT in the treatment of asthma, with the expectation of success.

46. However, the board firstly observes that at the publication date of document E80 (June 1985), IgE-stimulated histamine release from mast cells was merely one of the many possible factors, cells, aetiologies and mediators possibly underlying the pathophysiology of asthma (see Fig. 1 of document E78, published more than four years later than document E80), i.e., the skilled person was still uncertain as to the decisive inflammatory cascade underlying asthma and did not consider that IgE-mediated mast cell degranulation was the critical event in the pathogenesis of asthma. Secondly, document E80 (see last sentence of the abstract and page 6, third paragraph) reports that severe attacks of bronchial asthma were associated with raised levels of AAT in the blood or in local lesions. This finding was thus no incentive for the skilled person to supply further AAT, either by iv injection or by local application to a patient suffering from such an attack of bronchial asthma. Finally, it has not been disputed by appellants II and III that standard antihistamine medicaments were known to be ineffective for treating asthma, suggesting that inhibition of histamine release was not the target to be aimed at in the treatment of asthma. Therefore, the combination of document E2 or E16 with documents E80 does not render obvious the medical use of claim 1, either.
47. Appellants II and III depart from document E2 or E16 as closest prior art (see point 30 supra), relating to the use of AAT for treating emphysema (document E2) or chronic obstructive pulmonary disease (document E16). However, in accordance with the problem and solution approach, the Boards of Appeal have developed in their case law certain criteria for identifying the closest

prior art which provides the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be prior art relating to subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (c.f. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

48. The invention according to claim 1 serves the purpose to provide a medicament for treating asthma. In the light of the criteria elaborated by the Boards of Appeal for identifying the closest prior art, the most appropriate starting point for the objective assessment of an inventive step following the problem and solution approach is in the present case considered to be document E77, aiming at the same purpose as the present application, i.e. the treatment of asthma.
49. Document E77 indeed refers to asthma patients suffering from a genetic deficiency of AAT (see page 363, under "Introduction"). These AAT-deficient asthma patients have a predisposition to have asthma (c.f. the expression "hyperactive airways" on page 365, line 5 of document E77) and tend to have a more severe disease characterized by a less response to steroids, which is the medicament of choice (see document E4, page 365, lines 1-7 and document E39, r-h column, last paragraph).
50. The problem to be solved departing from this closest prior art is thus to find an alternative treatment to asthma. The proposed solution stated in claim 1 at issue is the topical treatment of asthma by means of

one or more serine protease inhibitors. In view of post-published document E60, showing the effectiveness of local administration (inhaled aerosol) of AAT in treating asthma, the board is satisfied that the above problem has been solved.

51. The relevant question is whether or not the above alternative treatment of asthma follows in an obvious manner from document E77, taken alone or in combination with other prior art documents. The board already decided (see points 33 and 34 supra) that the skilled person departing from document E77 would not use topical AAT therapy in the mild genetic deficiency associated with this form of asthma disclosed in this document because (i) this would represent a breach of the current dogma at that time, (ii) there was no suggestion in document E77 to treat this form of asthma with AAT and (iii) administration of AAT to the site of the disease was not contemplated. In the board's judgement, reasons (i) to (iii) above would also dissuade the skilled person from using topical AAT therapy in asthma implicated by mast cells and their mediators according to claim 1 at issue.

Skin diseases

52. Insofar as claim 1 relates to skin diseases, the board agrees that documents E81, E82 and E83, dealing with the treatment of psoriasis, represent the closest prior art. Appellants II and III maintain that claim 1 lacks an inventive step in view of this prior art. However, these documents merely disclose that there is a link between AAT deficiency and the manifestation of an inflammatory skin disease, namely psoriasis, and that

increased AAT activity was a characteristic of symptom-free psoriasis. It can also be derived from these documents that neutrophils and one of their mediators, elastase, were the main group of cells and mediators involved in psoriasis. Therefore, the skilled person departing from documents E81, E82 and E83 taken alone or in combination would not arrive at the medical use of claim 1, relying on the blockage of the inflammation cascade produced by mast-cells and their mediators with AAT applied topically at the site of the skin diseases.

53. In conclusion, the subject-matter of claim 1 and dependent claims also satisfies the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent as amended in the following version:
 - claims 1 to 7 of the main request filed during the oral proceedings;
 - pages 2 to 8 of the description filed during the oral proceedings.

The Registrar:

Chair:

P. Cremona

U. M. Kinkeldey