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Datasheet for the decision of 18 November 2005

Case Number: T 0531/04 - 3.3.04

Application Number: 98306332.2

Publication Number: 0903148

IPC: A61K 38/21

Language of the proceedings: EN

Title of invention:
Combination therapy for eradicating detectable HCV-RNA in patients having chronic hepatitis C infection

Patentee:
SCHERING CORPORATION

Opponents:
Alfa Wassermann S.p.A.
Teva Pharmaceutical Industries Ltd.
Sandoz GmbH
Appelt, Christian W.
Meduna Arzneimittelfabrik GmbH

Headword:
Combination therapy for HCV/SCHERING

Relevant legal provisions:
EPC Art. 123(2), 123(3), 52(4), 54, 56, 87(4), 112(1)

Keyword:
"Objection under Art. 123(3) EPC (not admitted); right to priority (no); inventive step (no); referral to the EBA (no)"

Decisions cited:
T 0155/85, T 0566/91, T 0207/94

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0531/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 18 November 2005

Appellant: (Patentee)
SCHERING CORPORATION
2000 Galloping Hill Road
Kenilworth, NJ 07030 (US)

Representative:
HOFFMANN EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
D-81925 München (DE)

Respondents:
(Opponent 02)
Alfa Wassermann S.p.A.
Via Ragazzi del'99, 5
I-40133 Bologna (IT)

Representative:
Hiebl, Inge Elisabeth
Kraus & Weisert
Patent- und Rechtsanwälte
Thomas-Wimmer-Ring 15
D-80539 München (DE)

(Opponent 03)
Teva Pharmaceutical Industries Ltd.
5 Basel Street, P.O. Box 3190
Petah Tiqva 49131 (IL)

Representative:
Nachshen, Neil Jacob
D Young & Co
21 New Fetter Lane
London EC4A 1DA (GB)

(Opponent 04)
Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl/Tirol (AT)

Representative:
Breuer, Markus
Breuer & Müller
Patentanwälte
St.-Paul-Strasse 9
D-80336 München (DE)

(Opponent 05) Appelt, Christian W.
c/o Forrester & Boehmert
Pettenkoferstrasse 20-22
D-80336 München (DE)

Representative: Engelhard, Markus
Forrester & Boehmert
Pettenkoferstrasse 20-22
D-80336 München (DE)

(Opponent 06) Meduna Arzneimittelfabrik GmbH
Ernst-Grote-Strasse 23
D-30916 Isernhagen (DE)

Representative: Merkle, Gebhard
TER MEER STEINMEISTER & PARTNER GbR
Patentanwälte
Mauerkircherstrasse 45
D-81679 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 23 February 2004 revoking European patent No. 0903148 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: R. Moufang
Members: R. Gramaglia
B. Claes

Summary of Facts and Submissions

I. European patent No. 0 903 148 (application No. 98 306 332.2) filed on 7 August 1998, claiming priorities from US 938033 of 21 September 1997 (document P1) and US 935123 of 22 September 1997 (document P2) and relating to a combination therapy for eradicating detectable HCV-RNA in patients having chronic hepatitis C infection was granted on the basis of 10 claims, of which independent claims 1 to 3 read as follows:

"1. The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of interferon alpha for a time period of 40-50 weeks, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy, characterised in that the patient has a viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR of a HCV genotype type 1 infection."

"2. The use of interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of interferon alpha in association with an effective amount of ribavirin for a time period of 40-50 weeks, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy, characterised in that the patient has a

viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR of a HCV genotype type 1 infection."

"3. The use of both ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of interferon alpha for a time period of 40-50 weeks, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy, characterised in that the patient has a viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR of a HCV genotype type 1 infection."

Dependent claims 4 to 10 related to specific embodiments of the use according to the above claims.

II. Notices of opposition were filed by opponents 01 to 06 requesting the revocation of the European patent on the grounds of Articles 100(a), (b) and (c) EPC. Opponent (01) withdrew its opposition by letter dated 29 July 2003. By their decision the opposition division revoked the patent because the subject-matter of the claims as granted (main request) infringed Article 123(2) EPC and that of the auxiliary request then on file lacked an inventive step.

III. The appellant (patentee) filed an appeal against the decision of the opposition division.

IV. With letter dated 17 October 2005, the appellant filed inter alia auxiliary request I consisting of claims 1 to 10, which was identical to the auxiliary request before the opposition division, and which was made the main request during the oral proceedings held on 17 and 18 November 2005 before the board. In claims 1 to 3 of this request, the wording "for a time period of 40-50 weeks" had been amended to read "for a **total** time period of 40-50 weeks" (emphasis by the board). During these oral proceedings, the appellant also filed the following questions of law to be referred to the Enlarged Board of Appeal:

I "Can a patent be revoked under Article 56 EPC on the basis of claims which, for example in the pharmaceutical field specify the patient, therapy regimen and specific disease, and which have been found to meet the requirements of Article 123 EPC, by not allowing subsequent evidence supporting such claims?"

II 1) "Can the burden of proof regarding the merit of the subject matter of claims of a granted patent that have been found to be admissible under Article 123 EPC, which merit has been confirmed by a decision of the Opposition Division be put on the appealing patentee in Appeal proceedings in assessment of Inventive Step?"

2) "If question 1) is answered in the affirmative can a subsequent report filed by patentee supporting the merit of the claims be disconsidered?"

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

D2 Reichard 0. et al., Hepatology, Vol. 26, No. 3, Suppl. 1, pages 108S-111S (1997);

D4 Bellobuono A. et al, J. Viral Hepatitis, Vol. 4, pages 185-191 (1997);

D9 Lurie Y. et al., Abstract from American Gastroenterological Association Digestive Disease Week, Meeting in Washington (May 1997);

D18 EP-A-0 707 855;

Dl9 Brouwer J.T. et al., J. Hepatology, Vol. 21, Suppl. 1, page S17 (1994);

D20 Chemello L. et al., J. Hepatology, Vol. 21, Suppl. 1, page S12 (1994);

D22 News Release, ICN Pharmaceuticals Inc. (18 May 1998);

D29 Lurie Y. et al., J. of Hepatology, Vol. 26, Suppl. 1, page 233 (1997);

D34 Lau J.Y.N. et al., The Lancet, Vol. 341, Issue 8859, pages 1501-1504 (1993);

D35 Orito E. et al., J. Med. Virol., Vol. 44 No. 4, pages 410-414 (1994);

D37 Yamada G. et al., Hepatology, pages 1351-1354 (November 1995);

D41 Heathcote J., Rev. Gastroenterol. Méx., Vol. 61, No. 4, Suppl. 2, pages S71-S75 (1996);

D42 Keeffe E.B. et al., Hepatology, Vol. 26, No. 3, Suppl. 1, pages 1O1S-107S (1997);

D45 Kasahara A. et al., Hepatology, Vol. 21, No. 2, pages 291-297 (1995);

D54 Di Bisceglie A.M. et al., Hepatology, Vol. 33, No. 3, pages 704-707 (2001);

D55 Munoz S. et al., Digestive Diseases Week and the 99th Annual Meeting of the American Gastroenterological Association, New Orleans, Louisiana, USA, Abstract No. L0444 (16-22 May 1998);

D56 De Bac C. et al., 33rd Annual Meeting of the European Association for the Study of the Liver, Lisbon, Portugal, 15-18 April 1998; Abstract No. P/C06/061;

D57 Kwo P.Y. et al., Digestive Diseases Week and the 99th Annual Meeting of the American Gastroenterological Association, New Orleans, Louisiana, USA, Abstract No. L0344 (16-22 May 1998);

D58 Buti M. et al., 48th Annual Meeting of the American Association for the Study of Liver

Diseases, Chicago, Illinois, USA, 7-11 November 1997; Abstract No. 351;

D59 Bassit L. et al., 48th Annual Meeting of the American Association for the Study of Liver Diseases, Chicago, Illinois, USA, 7-11 November 1997; Abstract No. 353;

D60 Vega P. et al., 33rd Annual Meeting of the European Association for the Study of the Liver, Lisbon, Portugal, 15-18 April 1998; Abstract No. P/C06/044;

D64 Declaration of Prof. B.R. Bacon dated 3 February 2003 (submitted by appellant);

D81 "Diseases of the Liver and Bile Ducts; A Practical Guide to Diagnosis and Treatment", Edited by Wu G.Y. and Israel J., Humana Press, Totowa, New Jersey, USA, pages 138-139 (1 July 1998);

D84 Ouzan D. et al., J. Hepatology, Vol. 25, Suppl. 1, Abstract C01/037, page 150 (1996).

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

Priority rights (Article 87(4) EPC)

- The Table on page 18 of the appellant's submissions dated 17 February 2003 showed that all the features of claim 1 at issue could be derived from priority document P2 (see page 2, line 25 to page 3, line 2

and claim 11 combined with page 7, lines 1 to 17 and page 10, lines 22 to 28 combined with page 20, lines 12 to 15).

Novelty (Article 54 EPC)

- The claimed subject matter was novel over the disclosure of documents D9, D18, D55, D56, D57, D59 and D60, which failed to identify a patient sub-group as recited in the claims, let alone in combination with a treatment period of 40-50 weeks in total.

Inventive step (Article 56 EPC)

- The core of the invention was the technical teaching resulting from the combination of claims 1, 5, 7 and 12 as filed. Further evidence (see documents D54 and D64) was provided in support of this original teaching. These documents clearly demonstrated that patients who did not respond to a previous course of therapy with interferon-α ("non-responders"), and who were infected with the genotype type 1 virus with an initial (pre-treatment) viral load (VL) > $2x10^6$ copies/ml serum benefited most from a prolonged treatment (40-50 weeks) of combination therapy, as shown by a higher rate (23%) of sustained viral response (SVR) (i.e., the eradication of the virus from the patients' serum, as confirmed by the absence of detectable serum HCV RNA for at least 24 weeks after the end of treatment (EOT)) in comparison to the rate of SVR (11%) of the same patient cohort treated for 24 weeks only. This patient cohort was considerably more refractory to

treatment than that of patients infected with other genotypes and having a VL below this baseline.

- Document D58 represented the closest prior art since it disclosed a patient sub-group as recited in the claims.

- The object of the present invention was to provide an improved therapy for a defined patient cohort, namely genotype 1-infected patients who were non-responders to a previous course of therapy with interferon-α monotherapy and had an initial viral load > $2x10^6$ copies/ml, thereby avoiding to treat other patients for whom the therapy was not beneficial.

- Combining the teachings of one or more of the prior art documents would not have led the skilled person to the present invention in an obvious way because these documents related to incomplete, non-conclusive studies performed on unidentified patient sub-groups. Therefore, the trials described in these documents could not allow any prediction to be made as to whether or not, e.g. a one-year (52 weeks) treatment according to document D55 would bring about any therapeutic improvement over the known 24-week long treatment, in terms of SVR, also because EOT data were not predictive of SVR.

- It was not scientifically correct to extrapolate results from the mono-therapy with interferon-α alone to the combination therapy with interferon-α + ribavirin.

VII. The submissions by the respondents (opponents 02 to 06), insofar as they are relevant to the present decision, can be summarized as follows:

Article 123(3) EPC

– The term "total" in the feature "for a total time period of 40-50 weeks" in present claim 1 meant that this "total" treatment period could be split in sub-periods separated by interruptions or different treatments, to yield a "sliced" treatment similar to that disclosed in document D42, (see page 102S, l-h column: "These patients were re-treated"), an embodiment not covered by granted claim 1. There had been thus a broadening of the scope of protection.

Priority rights (Article 87(4) EPC)

– The feature "for a total time period of 40-50 weeks" could not be directly and unambiguously derived from any of priority documents P1 or P2.

Novelty (Article 54 EPC)

– The feature in claim 1 "wherein the patient is one having failed to respond to a previous course of interferon alpha therapy, characterised in that the patient has a viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR of a HCV genotype type 1 infection" failed to provide a single distinguishing technical feature to the claim. Therefore, the claimed subject matter lacked novelty over the disclosure of documents D9, D18, D55, D56, D57, D59 or D60.

Inventive step (Article 56 EPC)

- There was neither a disclosure in the application as filed of solving the problem to provide an improved therapy for the patient cohort defined in present claim 1, nor was it possible to derive from the application as filed the technical effect emphasized by the appellant. Therefore, a reformulation of the technical problem to be solved as done by the appellant could not be done, also because said redefinition contradicted earlier statements in the application about the general purpose and character of the invention.

- The high viral load and the HCV genotype 1 were implicit features of any non-responder patient. Therefore, these features of present claim 1 had no distinguishing power over the relapser and non-responder patients dealt with in the prior art trials.

- Taking as closest prior art document D55, relating to the treatment with interferon-α and ribavirin of a patient cohort consisting of non-responders and relapsers having a VL > $2x10^6$ copies/ml and HCV genotype 1, the objective problem to be solved was the optimization of the duration of treatment. The solution thereto was treating for a total time period of 40-50 weeks. Since document D55 showed that a one-year trial led to the elimination of the circulating HCV-RNA in a substantial portion of relapser and non-responder patients, no inventive

step could be seen in reducing the duration of therapy from one year (52 weeks) to 40-50 weeks.

- Starting from document D58 as closest prior art, which disclosed the treatment with interferon-α and ribavirin over 24 weeks of a non-responder cohort of patients infected with the genotype 1 virus and having a basal viremia of 5.1 or $2.7x10^6$ copies/ml, the problem was to extend the treatment for these patient cohort (identical to that recited in claim 1) from 24 weeks to 48 weeks. However, from the Table in document D58, the skilled person would conclude that viremia decreased in function of treatment duration. There was thus an incentive to apply a longer therapy, as also suggested by documents D18, D57 and D59.

- Taking as closest prior art document D4, relating to the treatment with interferon-α and ribavirin of the same patient cohort as in present claim 1 consisting of non-responders and relapsers, the skilled person would be motivated to prolong the duration of treatment in view of the encouraging results of Table 4 of document D4 (see page 189) and document D9.

- According to paragraph [0020] of the patent in suit, the patient having failed to respond to a previous course of interferon-α therapy was a relapser or a non-responder. Therefore, even if the later evidence provided by documents D54/D64 showed the presence of an inventive step for the non-responders, the same conclusion could not be drawn for the relapsers.

VIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of claims 1 to 10 filed with letter dated 17 October 2005 as auxiliary request I (main request) or, in the alternative, that the questions filed in the oral proceedings (see section IV above) be referred to the Enlarged Board of Appeal (auxiliary request).

The respondents requested that the appeal be dismissed (main request) or, in the alternative, that questions of law with respect to the interpretation of Article 52(4) EPC be referred to the Enlarged Board of Appeal (auxiliary request).

Reasons for the Decision

Article 123(2) EPC

1. Claim 1 finds a basis in the combination of claim 1 ("interferon-α + ribavirin for treating patients non-responder to a previous course of interferon-α therapy"), claim 5 ("viral load > 2,000,000), claim 7 ("genotype type 1") and 12 ("for a total time period of 40-50 weeks") as filed. The claims thus satisfy the requirements of Article 123(2) EPC. None of the respondents raised any objection under this Article.

Article 123(3) EPC

2. One of the respondents (opponent 04) sought to argue that the feature "for a total time period of 40-50 weeks" in present claim 1 meant that this total period

could be split in sub-periods separated by interruptions or unrelated treatments, to yield a "sliced" treatment similar to that disclosed in document D42, (see page 102S, l-h column: "These patients were re-treated"). Hence, since claim 1 as granted did not cover this embodiment, there had been a broadening in the scope of protection.

3. The above objection under Article 123(3) EPC was raised only at a very late stage of the proceedings, namely during the oral proceedings before the board of appeal, although the appellant had introduced the claims of the present main request already as an auxiliary request before the opposition division and again with the grounds of appeal. Under these circumstances, the board would be prepared to use its discretion to admit the late-filed objection into the proceedings only if the objection were prima facie highly pertinent. However, the board is unable to accept that the wording "for a total time period of 40-50 weeks" in present claim 1 is a clear invitation to "slice" the treatment period of 40-50 weeks, while the language "for a time period of 40-50 weeks" in granted claim 1 implied no such invitation. The term "total" rather represents a restriction over granted claim 1, in the sense that it requires not to go beyond the 50 week end-point. In conclusion, no prima facie case of infringement of Article 123(3) EPC has been made out. Therefore the board does not admit this objection into the proceedings.

Priority rights (Article 87(4) EPC)

4. The board considers that neither priority document P1 nor P2 teaches treating with interferon-α + ribavirin the specific sub-group of HCV patients having failed to respond to a previous course of interferon-α therapy and having an initial VL > $2x10^6$ copies/ml and genotype type 1 infection, in combination with a length of treatment of 40-50 weeks, let alone 40-50 weeks in total. Even if, contrary to the case law, the priority documents could be treated as "reservoirs" for drawing any combination of claim features, the priority documents P1 or P2 do not contain any literal basis for the term "total", let alone for the wording "for a total time period of 40-50 weeks".

5. For these reasons, the claimed priority is not valid and the effective date for the purpose of Article 54(2) EPC is the filing date of 7 August 1998.

Novelty (Article 54 EPC)

6. Claim 1 is directed to a further medical use of ribavirin and has been formulated in the so-called "Swiss claim" format. It contains features which relate to the administration of ribavirin ("in association with interferon alpha", "for a total time period of 40-50 weeks") and to a certain class of patients, i.e. patients "having failed to respond to a previous course of interferon alpha therapy" and "having a viral load > 2,000,000 copies per ml of serum ... of a HCV genotype type 1 infection". Some of the respondents have argued that these features should not be taken into account for the assessment of novelty and

inventive step since they relate to medical methods excluded according to Article 52(4) EPC or do not constitute true distinguishing technical features.

7. The board considers that the above arguments raise serious legal questions to which the case law of the boards of appeal has not yet provided a completely uniform response. It furthermore notes the auxiliary request of the respondents to refer questions of law with respect to the interpretation of Article 52(4) EPC to the Enlarged Board of Appeal. However, for the purposes of the present decision, this issue need not be addressed since even if it were to be decided in favour of the appellant, the appeal still has to be dismissed for lack of inventive activity of the claimed subject-matter (see points 8-43 below). The board therefore refrains from deciding the novelty of the claimed subject-matter and furthermore, without deciding this issue, assumes for the benefit of the appellant that, in the context of the assessment of inventive activity, all of the above-mentioned features of claim 1 have to be taken into account.

Inventive step (Article 56 EPC)

Closest prior art

8. Claim 1 is concerned with a combination therapy (interferon-α + ribavirin) applied for a total time of 40-50 weeks to eradicate detectable HCV-RNA in patients having chronic hepatitis C infection, wherein the HCV patients are those having failed to respond to a previous course of interferon-α monotherapy (i.e., they are "relapsers" and "non-responders"; see paragraph

[0012] of the patent in suit) and having a initial (pre-treatment) viral load (VL) of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR of a HCV genotype type 1 infection. Otherwise stated, claim 1 pertains to a correlation between, on the one hand, treating with the above combination a specific subgroup of HCV patients (relapsers and nonresponders with VL > $2x10^6$ copies/ml and genotype type 1 infection) and, on the other hand, a length of treatment (40-50 weeks in total).

9. According to paragraph [0013] of the patent in suit, HCV patients belonging to the above cohort are "difficult to treat patients".

10. The appellant maintains that there is a functional relationship between the particular physiological and pathological status of the above patient cohort and the therapeutic effect achieved when the combination (interferon-α + ribavirin) is applied for a total time of 40-50 weeks. To buttress the above view, the appellant relies on post-published document D54 and declaration D64 to show that there is a higher rate (23%) of sustained viral response (SVR), i.e., eradication of the virus from the patients' serum, as confirmed by the absence of detectable serum HCV RNA for at least 24 weeks after the end of treatment (EOT) for the patient cohort referred to in claim 1 after a 40-50 week combination therapy, in comparison to the rate of SVR (11%) of the same patient cohort treated for 24 weeks only (see "SVR" in the Table in paragraph 6 of declaration D64). Another way to define the technical effect emphasized by the appellant is that the sub-cohort referred to in claim 1 gets the

most benefits in terms of increase of the rate of SVR from prolonging the combination therapy from 24 weeks to 48 weeks.

11. During the oral proceedings, the parties were not in agreement as to whether document D55 or document D58 represented the closest prior art. The former relates to a planned one-year trial of the combination therapy (interferon-α + ribavirin) performed on a HCV cohort comprising 110 patients (relapsers and non-responders) exhibiting an initial **average** VL = 3.4×10^6 copies/ml and comprising 77.5% of patients infected with the virus of type 1 genotype (see "genotypes 1a or 1b"). The provisional result reported in this document is that 53% of the patients who had completed 6 months of therapy became non-viremic (EOT_{6m} = 53%). It is also stated in document D55 that the virologic evaluation will also be made "the 12 months following completion of therapy". Therefore, this study purported first to determine the rate of EOT response after completion of the one-year trial, then the rate of SVR within the following 12 months.

12. Document D58 relates to a 24-week study of the combination therapy (interferon-α + ribavirin) given daily (QD) vs. three times in a week (TIW) to 10 patients (non-responders) infected with the type 1 genotype. The 5 patients of the QD group had an **average** initial VL = 5.1×10^6 copies/ml for QD, whereas the 5 patients of the TIW group had an **average** initial VL = 2.7×10^6 copies/ml. According to the provisional results reported in document D58, the patients who achieved a 2 log reduction in serum HCV RNA by week 4 (1/5 of the TIW patients and 3/5 of the QD patients)

were also HCV RNA negative by week 8. The aim of this study was thus to establish which of the QD vs. TIW protocols was better in achieving viral reduction on a short term basis. The answer to this question lay in the title of this "poster", which suggested that the QD regimen was better (cf. "daily").

13. Since the viral loads for the QD and TIW groups are **average** VL's and having regard to a possible "skewing" effect (a patient has $5x10^6$, another $1x10^6$, the average is $3x10^6$), the board does not share the appellant's opinion that document D58 discloses a patient sub-group as recited in the claims and that hence it must represent the closest prior art.

14. While neither of the HCV patient cohorts disclosed in document D55 (relapsers and non-responders; 77.5% type 1; average VL = $3.4x10^6$ copies/ml) and document D58 (non-responders; 100% type 1; average VL_{QD} = $5.1x10^6$ copies/ml; average VL_{TIW} = $2.7x10^6$ copies/ml) appear to come closer than the other to the patient cohort recited in claim 1 (relapsers and non-responders; 100% type 1, $VL_{each\ patient} > 2x10^6$/ml), the final result aimed at by the study in document D55, namely that of determining the rate of SVR after one year therapy and its follow-up, is closer to the claimed subject matter (cf. "to eradicate detectable HCV-RNA" in present claim 1) than the QD vs. TIW issue dealt with in document D58. In conclusion, document D55 represents the closest prior art by virtue of a similar purpose which requires the minimum of structural and functional modifications.

15. One of the respondents (opponent 02) considered document D4 to represent the closest prior art. This document relates to a six month trial and a six month follow-up with interferon-α and ribavirin carried on a patient cohort consisting of non-responders and relapsers. However, no pre-treatment viral loads are reported in this document, nor is there any suggestion to lengthen the therapy to one year and its follow-up (see document D55). In conclusion, this document is more remote than document D55.

The objective technical problem

16. The problem to be solved by the claimed subject-matter in the light of the disclosure of document D55 is thus to identify among the patients of document D55 (see point 11 supra) a sub-cohort which could get the most benefits in terms of increase of the rate of SVR from a longer treatment regime. The solution proposed in present claim 1 is treating **only** the sub-cohort of non-responders or relapsers of document D55, who are (each) infected with the type 1 genotype and have (each) a VL > $2x10^6$ copies/ml of serum (as measured by HCV-RNA quantitative PCR), with a combination therapy (interferon-α + ribavirin) for a total time of 40-50 weeks.

17. The respondents have objected to the above formulation of the technical problem. It was argued that there was neither a disclosure in the application as filed of the above problem nor was it possible to derive from the application as filed the technical effect emphasized by the appellant (see point 10 supra). Reformulation of

the objective problem as proposed was therefore not allowable.

18. The board, however, observes on the basis of established case law that the proper yardstick for defining a problem, namely the ultimate technical effect, is what is actually achieved vis-à-vis the closest prior art.

19. It is true that the technical effect invoked by the appellant (see point 10 supra) cannot be derived from the application as filed in order to apply the problem-solution approach. However, later filed evidence may in principle be accepted in support of the presence of an inventive step, provided this evidence is related to the original problem to be solved in the application as filed.

20. As regards the original problem in the application as filed, the skilled person would recognize that one of the goals aimed at (see paragraph [0013]) was obtaining a SVR (i.e., a durable eradication of the virus from the patient's blood, as confirmed by the absence of detectable HCV RNA from the serum for at least 24 weeks after the end of treatment (EOT)) in difficult to treat HCV patients, namely those infected with the virus of genotype type 1 and having a VL > $2x10^6$ copies/ml. Therefore, since the advantage invoked by the appellant (technical effect) is related to the original problem, the board assumes in the appellant's favour that a more exact definition of the original problem can be given, even in the course of the present appeal proceedings (see e.g., decision T 566/91 of 18 May 1994, point 5.2).

21. The respondents further argue that the redefinition of the technical problem should not contradict earlier statements in the application about the general purpose and character of the invention (cf. decision T 155/85, OJ EPO 1988, 87). However, the board does not see this contradiction pointed out by the respondents. It is true that paragraph [0013] of the application as filed (corresponding to a combination of claims 1, 5, 7 and 11 as filed) related to a 20-30 week treatment period for this patient cohort and that paragraph [0063] showed that this cohort had the poorest SVR, however, the skilled person would recognize from claim 12 as filed that the 20-30 week time period referred to in paragraph [0013] and claim 11 could be prolonged to a total time of 40-50 weeks, i.e., the subject matter now claimed.

Has the problem been solved?

22. The board notes that the question arises whether or not the problem highlighted under point 16 supra has actually been solved by the claimed subject matter. The appellant relies on post-published document D54 and declaration D64, the latter being a retrospective study of the results reported in the former document, to show that a technical effect follows from the features in present claim 1 (see point 10 supra). However, the board observes that the patient cohort dealt with in document D54 are the **non-responders** (see the title), whereas present claim 1, interpreted in the light of paragraph [0012] of the description and of the Examples of the patent in suit (see paragraph [0025], line 16: "who had relapsed") relates to both the relapsers and the non-responders.

Relapsers

23. Therefore, insofar as the claimed subject matter deals with relapsers, no evidence is before the board that the problem of providing a better treatment to the relapsers of document D55 without unduly increasing the exposure of a portion of these patients to the drug mixture, or any other technical problem has been solved.

24. Hence it may be concluded that an embodiment (here: "the relapsers") falling under the scope of claim 1 lacks inventive step for failure to solve any problem. This would mean that the claim as a whole and the request containing it already fail on this deficiency. However, since the discussion at the oral proceedings before the board was not primarily focussed on this issue but rather on the non-responder embodiment, the board considers it appropriate to base the reasons for the decision primarily on the latter embodiment.

Non-responders

25. Turning to the claimed subject matter, insofar as it relates to non-responders, the technical effect following from the features of present claim 1 (see point 10 supra) deserves a detailed analysis.

26. Document D54 cited by the appellant in support of the invoked technical effect investigates, inter alia, the effect of a 24-week treatment vs. a 48-week treatment with the combination therapy (interferon-α + ribavirin) given to non-responder patients. The relevant technical effect derivable from this document is an overall

increase in the rate of SVR for non-responders taken **collectively** (i.e., regardless of any stratification on the viral load and/or the genotype), upon prolonging the combination therapy from 24 to 48 weeks (see page 705, l-h column, third paragraph of document D54: "Interestingly, however, the relapse rate was much higher in the group treated for only 24 weeks compared with the 48-week group" and page 706, r-h column, lines 12-16: "Patients treated for 48 weeks had a significantly lower rate of relapse after stopping therapy than those treated for a shorter period, suggesting that longer treatment should be used for IFN nonresponders").

27. Besides this collective (unstratified) group of non-responders, document D54 is silent as to a possible increase in the rate of SVR after a 48 week-treatment compared to a 24 week-treatment with the combination therapy for the specific difficult to treat sub-cohort of non-responders infected with the type 1 genotype and having an initial VL > $2x10^6$ copies/ml of serum (see points 8 and 9 supra). This is because the non-responder patients of document D54 have a wide range of viral loads inside and outside the teaching of present claim 1 and are infected by HCV of genotypes type 1, 2, 3, etc (see declaration D64, paragraph 8). Moreover, document D54 does not address any stratification of the non-responder patients on the combination of the two virological factors genotype type 1 **and** VL > $2x10^6$ copies/ml (see ibidem: "a group not specifically discussed in the attached article"), let alone any correlation between this stratification (sub-cohort) and the rate of SVR at 24 weeks vs. 48 weeks.

28. Nevertheless, an increase in the rate of SVR in the specific sub-cohort of non-responders infected with the type 1 genotype and having a VL > $2x10^6$ copies/ml of serum after a 48 week-treatment with the combination therapy compared to a 24 week-treatment does turn up in the Table in paragraph 6 of declaration D64 (see "SVR": 23% vs. 11%), after the author of declaration D64 "reviewed the information compiled in our studies" (see ibidem, paragraph 6) and presented data correlating said stratification of non-responder patients (characterized by the genotype type 1 **and** VL > $2x10^6$ copies/ml) with the rate of SVR at 24 weeks vs. 48 weeks. As already indicated under point 10 supra, the above Table in declaration D64 shows that the latter non-responder sub-cohort gets the most benefits in terms of increase of the rate of SVR from prolonging the combination therapy from 24 weeks to 48 weeks.

29. In conclusion, there is sufficient evidence before the board to make it credible that the problem of identifying among the **non-responder** patients of document D55 a sub-cohort which could get the most benefits in terms of increase in the rate of SVR from a longer treatment regime, has been solved.

30. The relevant question, in the context of the non-responder patients, therefore is whether or not the skilled person, starting from document D55 and facing the above problem, would have arrived at the claimed subject matter in an obvious way.

31. At the filing date of the patent in suit, it was known from document D41 (see page S-71, r-h column, line 6 from the bottom to page S-72, l-h column, line 4),

document D42 (see Table 2 on page 104S) and document D45 (see page 295, r-h, second full paragraph) relating to the mono-therapy with interferon-α alone that the rate of SVR in non-responders depended on the duration of therapy and that an increase in the rate of SVR took place by extending the duration of therapy with interferon-α to a full year.

32. As regards the treatment of HCV patients with the combination interferon-α + ribavavirin, those working in the field held that extending the duration of the combination therapy was likely to achieve a similar effect (see e.g., document D19: "The proportion of sustained response might be further increased by modification of dosage and duration of the combination"). Hence, there was an incentive in the prior art to conduct clinical trials for **all HCV patients groups** (including the non-responders covered by present claim 1) for 6 and 12 months (see document D2, page 111S, l-h column, second full paragraph) and to see what happened. Indeed several one-year trials were under way (see e.g., documents D29, D55 and D56). Therefore, although none of the above documents reported results of a complete 48-week trial **and** its follow-up performed on a cohort of non-responder patients, the situation was one where it was "obvious to try". It remains to be examined whether or not there was a "reasonable expectation of success" that prolonging the combination therapy would achieve (i) an **overall** (i.e., regardless of any stratification on the viral load and/or the genotype) increase in the rate of SVR in the (unstratified) cohort of non-responders of document D55, and would also achieve (ii) the most

benefits in the (stratified) non-responder sub-cohort having the genotype type 1 and a VL > $2x10^6$ copies/ml.

33. The approach to inventive step which involves assessing whether or not the skilled person had a "reasonable expectation of success" has to take into account the real difficulties which could have been foreseen in performing the necessary experimental steps at the priority date, or the concerns which would have prevented the skilled person from entering the way towards the claimed subject matter. According to decision T 207/94 (OJ EPO 1999, 273), points 38 and 44 and headnote, any allegation of features putting in jeopardy reasonable expectation of success must be based upon technical facts. When using this approach for other biological inventions such as in the case at issue, the same rationale must apply.

34. As regards the "reasonable expectation of success" by the skilled person with regard to the technical effect (i) above, namely the overall increase in the rate of SVR in the (unstratified) cohort of non-responders, the board is not able to see any of these real difficulties or concerns. The appellant argues that the incomplete trials performed with the combination therapy on non-responders could not allow any prediction to be made as to whether or not a longer (e.g., a 40-50 week) treatment would bring about any therapeutic improvement in terms of sustained viral response (SVR). However, there was a common belief (see document D19, supra, see also document D22 (see fourth paragraph), dealing with naive patients) that a more aggressive therapy (longer therapy or with higher doses of either interferon-α or the combination) could turn

further non-responders into responders. In fact, obtaining a SVR also in this sub-group of HCV patients was believed to be a prerequisite for stopping the progression of the disease to cirrhosis and possibly to hepatocellular carcinoma (see document D4, page 185, l-h column, lines 1-4). What remained to be done was merely checking the follow-up results. The fact that the patentee has gone further down the road of these routine follow-up checks and found that (i) prolonging the combination therapy from 24 to 48 weeks achieves an increase in the rate of SVR in the cohorts of non-responders taken as a whole (see document D54 and point 27 supra) cannot be taken as evidence that there was not already a reasonable expectation of success derivable from the prior art, insofar as technical effect (i) above (overall increase) was concerned.

35. As for the "reasonable expectation of success" by the skilled person in respect of technical effect (ii) according to which the non-responder sub-cohort that gets the most benefits in term of increase of the rate of SVR from a longer therapy is that having the genotype type 1 and a VL > $2x10^6$ copies/ml (see declaration D64 and point 28 supra), the board observes the following.

36. At the filing date of the patent in suit, it was known that the non-responder HCV patient cohort included patients characterized by a wide range of viral loads spacing from a few hundred copies/ml to several million copies/ml, and with infections by HCV of genotypes 1, 2, 3, etc. (see e.g. document D34, page 1502, Fig. 2: "NR"; see also Fig. 1 on page 1352 of document D37, wherein

29 such patients lie between "Non-responder" and the abscissa).

37. It was also known that HCV patients infected with the HCV of genotype type 1 and/or having a high baseline VL were more difficult to treat than others, to the extent that these features were "predictors" of a poor SVR and that type 2 or 3 and/or low initial (pre-treatment) VL were "response factors" (see document D81, page 139, under "Patient Selection": "low pretreatment viremia level and HCV nongenotype 1 infection appeared to be independent favorable factors"; see also document D59: "55% of the pts infected with type 3 had ETR [End of Treatment Response; another acronym for EOT] against 31% of type 1 (P<0.01)", and document D20: "sustained response to IFN alone or to IFN plus ribavirin was observed in 55% of the cases with HCV-2 or HCV-3 but only in 12% of patient with HCV-1").

38. These difficult to treat sub-cohorts (type 1 and initial VL > $2x10^6$ copies/ml) were known to **prevail** among non-responders (see e.g. document D34, page 1502, Fig. 2: "NR"; see also Fig. 1 on page 1352 of document D37, wherein 20 of such patients lie between "Non-responder" and the dark area, and document D35, (see patients No. 27 to 35 (non-responders) in Table III on page 413). It is true that in some of these documents the HCV RNA levels, expressed in eq/ml, have been measured by the "bDNA assay" instead of HCV-RNA quantitative PCR as required by present claim 1, however, a correlation exists between these two techniques (see document D84).

39. Finally, the skilled person would have understood that the non-responders with genotype 2 or 3 and/or low initial VL in the above cohorts including the whole spectrum from easy to treat patients (with type 2 or 3 infection and VL < $2x10^6$ copies/ml) to difficult to treat patients (type 1 and VL > $2x10^6$ copies/ml) were likely to respond equally well to a milder therapy. The relative improvement after a further 24 weeks of treatment could thus be expected to be less for this sub-group, compared with a difficult to treat one. This fact was confirmed by document D2, page 1085, end of the l-h column: "the combination demonstrates clear-cut superiority only in patients with unfavorable profiles for a response to interferon, in particular patients with a high level of HCV RNA" and by document D45 (see page 295, r-h column, lines 12-14 from the bottom: "Moreover, the rate of sustained response was higher in type 1b with 52 weeks of therapy than with 28 weeks of therapy").

40. Therefore, the board considers that the skilled person would have concluded that the effect of a more aggressive (e.g., longer) therapy was mainly to increase the relative rate of SVR in the **prevailing** difficult to treat sub-cohort of HCV patients having type 1 genotype and initial VL > $2x10^6$ copies/ml.

41. In summary, in the light of the fact that difficult to treat sub-cohorts (type 1 and initial VL > $2x10^6$ copies/ml) prevailed among non-responders and the common general knowledge that a more aggressive (e.g., longer) treatment mainly turned further difficult (rather than easy) to treat patients into responders, the skilled person would have thus reasonably concluded

not only that an **overall** increase in the rate of SVR would be achieved for the non-responder cohort of document D55 upon prolonging the combination therapy from 24 to 48 weeks, but also that the sub-group thereof which would benefit most in terms of (relative) rate of SVR from extending treatment from 24 to 48 weeks was likely to include the sub-cohort of non-responders having the genotype type 1 and a VL > $2x10^6$ copies/ml.

42. In conclusion, the skilled person faced with solving the problem of identifying among the non-responder patients of document D55 a sub-cohort which could get the most benefits in terms of increase in the rate of SVR from a longer treatment regime, would have arrived in an obvious way at the measures proposed in claim 1, namely treating with the combination interferon-α + ribavirin a specific subgroup of HCV patients (nonresponders with VL > $2x10^6$ copies/ml and genotype type 1 infection) for a total of 40-50 weeks.

43. In view of the foregoing, the subject matter of claim 1 does not satisfy the requirements of Article 56 EPC.

Referral of questions to the Enlarged Board of Appeal

44. At the oral proceedings the appellant requested as an auxiliary request that the questions stated in section IV above should be referred to the Enlarged Board of Appeal if the board were not minded to allow the appeal. According to Article 112(1)(a) EPC, a board of appeal shall, during proceedings on a case, refer any question to the Enlarged Board of Appeal if it considers that a decision is required for the purposes

of ensuring uniform application of the law or clarifying an important point of law. In order to justify a referral, the question to be considered has to be relevant for the outcome of the proceedings of the board of appeal.

45. Two of the questions formulated by the appellant, i.e. the questions I and II 2, deal with the issue of allowing "subsequent" evidence in order to "support" claims which have been found to meet the requirements of Article 123 EPC. However, it follows from the reasons as set out above (cf in particular points 19, 20 and 29) that the board has not disallowed any post-published evidence brought forward by the appellant in order to assess the objective problem solved by the invention. The two questions are therefore not relevant for reaching a decision in the present case.

46. The further question II 1 formulated by the appellant relates to the burden of proof with respect to the requirement of inventive activity. While the board has come to the conclusion that, with respect to the patient sub-cohort of relapsers, there is no evidence to show that the problem of providing a better treatment without unduly increasing the exposure to the drug mixture has been solved (above point 24), the present decision is not primarily based on this conclusion. The decisive reason for the finding that claim 1 of the main request lacks inventive activity is that, with respect to the patient sub-cohort of non-responders, the skilled problem would have come to the claimed invention in an obvious way starting from document D55 as the closest prior art (above points

25-43). Therefore, the issue of burden of proof is of no relevance for the outcome of the present case.

47. The respondents also requested as an auxiliary request that certain questions of law with respect to the interpretation of Article 52(4) EPC (see above section VIII and point 7) should be referred to the Enlarged Board of Appeal. However, as the board has come to the conclusion that the appeal has to be dismissed in any event, i.e. irrespective of the possible answer to these questions, similarly, a decision of the Enlarged Board on these questions is not required for the outcome of the present appeal proceedings.

Order

For these reasons it is decided that:

1. The request of the appellant to refer questions to the Enlarged Board of Appeal is refused.

2. The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona R. Moufang