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**Datasheet for the decision
of 21 March 2012**

Case Number: T 1545/08 - 3.3.04
Application Number: 99303729.0
Publication Number: 956861
IPC: A61K 38/21, A61K 31/7056,
A61P 31/14
Language of the proceedings: EN

Title of invention:

Combination therapy comprising ribavirin and interferon alpha
in antiviral treatment naive patients having chronic
hepatitis C infection

Patentee:

Merck Sharp & Dohme Corp.

Opponents:

Alfa Wassermann S.p.A.
Teva Pharmaceutical Industries Ltd.
Sandoz GmbH
Krauss, Jan B.
Forrester & Boehmert

Headword:

Combination therapy HCV/MERCK SHARP & DOHME CORP.

Relevant legal provisions:

EPC Art. 111(2), 114(2)
RPBA Art. 13

Relevant legal provisions (EPC 1973):

EPC Art. 56

Keyword:

"Inventive step - (yes)"

Decisions cited:

T 0296/93, T 0860/93, T 0609/02, T 0531/04, T 1329/04,
T 1399/04, T 1599/06, T 0293/07, T 0847/07, T 0365/09

Catchword:

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Case Number: T 1545/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 21 March 2012

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted
4 July 2008 concerning maintenance of European
patent No. 956861 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Morawetz
G. Alt

Summary of Facts and Submissions

I. European patent No. 0 956 861, claiming priority from US 79566 (15 May 1998) was granted with claims 1 to 11.

II. Independent claim 1 as granted reads 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 wherein the pharmaceutical composition is for administering an effective amount of ribavirin in association with an effective amount of interferon alpha, characterised in that the ribavirin in association with the interferon alpha is for administration for a time period of 40-50 weeks, the patient is an antiviral treatment naïve patient, and the patient is one having a HCV genotype type 1 infection and a viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR."

Independent claim 2 refers to the use of interferon alpha (IFN- α) for the manufacture of a pharmaceutical composition for treating a chronic hepatitis C virus (HCV) infected patient to eradicate detectable HCV-RNA wherein the pharmaceutical composition is for administering an effective amount of IFN- α in association with an effective amount of ribavirin. Independent claim 3 relates to the use of both ribavirin and IFN- α for the same purpose. Dependent claims 4 to 9 further define the nature of the IFN- α , whereas dependent claims 10 and 11 define the dosages

- and dosing regimen of each component of the preceding claims.
- III. The patent has been opposed under Article 100(a) EPC 1973 on the grounds of lack of novelty (Article 54 EPC 1973), lack of inventive step (Article 56 EPC 1973) and because it did not relate to a patentable invention according to Article 52(4) EPC 1973 and under Article 100(c) EPC 1973 on the ground of added subject-matter (Article 123(2) EPC).
- IV. The opposition division decided that the grounds of opposition did not prejudice the maintenance of the European patent and rejected the oppositions under Article 102(2) EPC 1973 (hereinafter "first decision" of the opposition division).
- V. Appeals were lodged by opponents 01 to 04 against this first decision of the opposition division.
- VI. The board, in a composition different from the present one, decided in the first appeal proceedings (cf. T 1399/04 of 25 October 2006) that with regard to the question of inventive step the decision had been taken in violation of the appellants' (opponents') right to be heard as defined in Article 113(1) EPC 1973. The board also decided that the main request (patent as granted) fulfilled the requirements of Articles 123(2), 52(4) and 54 EPC 1973 and that its claims were entitled to the claimed priority. The case was remitted to the department of first instance for further prosecution.
- VII. In its second decision regarding the patent (hereinafter the "decision under appeal") the

opposition division decided that the main request (patent as granted) lacked an inventive step (Article 56 EPC) and that auxiliary requests 1 to 10 also failed to comply with the requirements of the EPC. Claims 1 to 6 of auxiliary request 11 were considered to fulfil all requirements of the EPC.

VIII. In the decision under appeal the opposition division confirmed the finding in its first decision that the subject-matter of the claims as granted was not obvious over the disclosure in documents (OD2) or (OD8) but held that it lacked an inventive step over the teaching of document (OD12), now considered to represent the closest prior art document, in combination with the disclosure in document (OD59).

IX. In an *obiter dictum* the opposition division observed that "[s]ince the patients in [document] OD12 are treated starting 3 to 24 months after transplantation (see p. 501 col. 2 last sentence of Patient characteristics) it would appear that they had not yet developed chronic hepatitis C when combination therapy was started. If this is confirmed it would throw a totally different light on [document] OD12 since it would not relate any longer to the same disease as the present claims."

X. Appeals were lodged by the patent proprietor (hereinafter appellant I) and opponents 02 to 04 (hereinafter appellants II-IV) against the second, interlocutory decision of the opposition division.

- XI. Appellants II, III and IV filed replies to the grounds of appeal filed by appellant I with letters dated 15 April 2009.
- XII. With a letter dated 15 June 2009 appellant I filed its reply to the grounds of appeal filed by appellants II, III and IV.
- XIII. A summons to oral proceedings was issued on 11 November 2011.
- XIV. With a letter dated 21 February 2012 appellant I filed document (D128).
- XV. With a fax dated and received 2 March 2012 appellant II filed document (D129).
- XVI. Oral proceedings were held before the board on 21 March 2012. Appellant IV did not attend oral proceedings as announced in its letter dated 20 March 2012.
- XVII. The following documents are mentioned in this decision:
- (OD1) Gastroenterology, vol. 111, 1996, pages 1307-1312
 - (OD2) Hepatology, vol. 26, No. 3, Supplement 1, 1997, pages 108S-111S
 - (OD3) The Lancet, vol. 351, January 1998, pages 83-87
 - (OD5) J. Hepatology, vol. 23, Supplement 2, 1995, pages 8-12
 - (OD8) EP-A-0 707 855
 - (OD12) Hepatology, vol. 26, 1997, no. 2, pages 500-504
 - (OD17) ICN Pharmaceuticals, News release, 18 May 1998
 - (OD19) Reichard/Weiland hepnet.com/nih/reich.html

- (OD30) *J. Hepatology*, vol. 21, 1994, supplement 1, S17
- (OD33) *Lakartidningen*, vol. 96, January 1998, pages 40-43
- (OD33a) English translation of (OD33)
- (OD43) *Annals of Internal Medicine*, vol. 123, 1995, pages 897-903
- (OD46) *Journal of Medical Virology*, vol. 44, 1994, pages 410-414
- (OD48) *Hepatology*, vol. 22, 1995, pages 1351-1354
- (OD50) *Hepatology*, vol. 26, 1997, pages 2S-10S
- (OD52) *Rev Gastroenterol Méx*, vol. 61, 1996, pages 71-75
- (OD53) *Hepatology*, vol. 26 (Suppl 1), 1997, pages 101S-107S
- (OD59) *Hepatology*, vol. 21, 1995, pages 291-297
- (OD60) *Hepatology*, vol. 22, 1995, pages 700-706
- (OD80) *Hepatology*, vol. 26, 1997, AASLD Abstract 231
- (OD83) *Hepatology*, vol. 26, 1997, AASLD Abstract 716
- (OD104) *Hepatology*, vol. 31, 2000, pages 211-218
- (OD106) Declaration by Professor Graham Foster, 2006
- (OD107) Declaration by Professor Howard J. Worman, 2006
- (OD108) Declaration by Dr. George Bird, 2006
- (OD110) *Fields Virology*, 1996, pages 1035-1058
- (OD112) *Hepatology*, vol. 26, 1997, AASLD abstract 1153
- (OD113) HepNet, Esteban-Mur, "Combination treatment in previously untreated patients"
- (OD116) World medical association declaration of Helsinki
- (OD121) Declaration by Professor Michael P. Manns, 2007
- (OD123) *Living with Hepatitis C*, 1997, R. English and G. Foster, pages 65-85
- (D128) *Hepatology*, vol. 20, 1994, pages 1137-1143
- (D129) HepNet "Update on Liver Disease and Hepatitis-

Issues and Controversies in 1997"

XVIII. The submissions by appellant I (patent proprietor), insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of document (D128)

In the *obiter dictum* in the decision under appeal the opposition division had stated that document (OD12) would not relate to the same disease as the claims of the main request, if the patients in document (OD12) had not yet developed chronic hepatitis C. Document (D128) was therefore highly relevant as it provided evidence that the vast majority of patients in document (OD12) did not have chronic hepatitis C.

Admissibility of document (D129)

Document (D129) had been filed inexcusably late. The response rates depicted in slide 8 were only estimates and in any case irrelevant as they contained no reference to HCV genotype 1 or to a high viral load. The document contained no proof for a sustained viral response (SVR). The data reported were end of treatment (EOT) data as could be deduced from the rebound of haemoglobin levels observed in slide 9, which effect was known to occur if a patient was taken off the therapy (see e.g. document (OD43)).

Binding effect of decision T 1399/04

The interpretation of the sentence bridging pages 110S and 111S in document (OD2) adopted by the board in

decision T 1399/04 was *res judicata* and binding on the present board.

Interpretation of claim 1

The opposition division's interpretation of "to eradicate" was contradictory to the dictionary definition of this word and also contradicted the teaching of the patent. The term "no detectable HCV-RNA" was defined in paragraph [0028] of the patent. To "eradicate" meant to completely get rid of detectable HCV-RNA. Eradication could not be measured during or at the end of antiviral treatment. Rather, the SVR had to be determined to evaluate whether the patient had eradicated the virus.

Paragraph [0025] of the patent did not provide a definition of chronic hepatitis C. The average skilled person would know the difference between acute and chronic hepatitis C.

Inventive step

Document (OD12) could not be considered to be the closest prior art document because it followed from the disclosure in document (OD12) on page 500, right hand column, first full paragraph; page 501, left column, line 11-14; Table 1; and page 503, right hand column, last full paragraph that the majority of the patients of document (OD12) did not have chronic hepatitis C, see also document (OD128), Figs. 1 and 2. There was no reason to believe that any of the 5 patients that were reported as HCV RNA negative (see paragraph bridging the columns on page 502) had chronic hepatitis C. In

document (OD12) ribavirin monotherapy continued indefinitely and this was considered to be crucial to avoid relapse, whereas in the patent the treatment ended after 40 to 50 weeks. There was also no indication that HCV-RNA was eradicated in any of the patients because all patients were still, at the time document (OD12) was written, undergoing ribavirin monotherapy to avoid relapse (page 503, right column, 4th paragraph). Since ribavirin was a known antiviral agent that suppressed viral replication (see e.g. document (OD43)), any "result" reporting patients who became "HCV-RNA negative" could only be considered as a preliminary indication because there was no way of determining whether a patient had truly eradicated HCV-RNA from the serum until the selective pressure imposed by ribavirin against viral replication had been removed from the patient.

Document (OD1) did not qualify as the closest prior art document because it only disclosed combination treatment for 24 weeks and stated that neither genotype 1 nor pre-treatment HCV RNA levels significantly affected the outcome of treatment with the combination for 24 weeks.

Document (OD8) failed to mention anything about HCV genotypes or viral load of the patients. It did not relate to the same purpose and contained only a passing comment on naïve patients. Appellant II itself had said of document (OD8) that it was a vague patent application that included no reference to convincing data in the area of ribavirin/interferon combination therapy of HCV.

There was no evidence on file that the content of document (OD19) belonged to the state of the art.

Document (OD43) could not be considered as the closest prior art document because it related to ribavirin monotherapy and did not identify the subgroup of patients with genotype 1 and greater than 2 million copies of HCV RNA/ml serum. It did not mention or contemplate the treatment of patients with a combination therapy for longer than 24 weeks.

Document (OD60) related to interferon monotherapy and could not represent the closest prior art. There was no indication in the document to use ribavirin in combination with interferon.

The common general knowledge that patients infected with HCV genotype 1 and a high viral load were difficult to treat did not represent a realistic spring board for the skilled person.

Document (OD2) might be considered to represent the closest prior art. Document (OD2) did not identify patients having a HCV infection genotype 1 and a high viral load as a distinct patient group, this was *res judicata* (see decision T 1399/04, point 34 of the reasons on page 25). Any problem solution approach starting from the assumption that document (OD2) disclosed this patient group was wrong. A cut-off value of greater than 2 million copies of HCV RNA was not a value that was in any way equated with "high" viral load in May 1998. In fact there was no commonly accepted definition of "high" viral load in the art.

Document (OD80), an abstract, was not common general knowledge. It analysed the HCV genotype and HCV RNA levels but did not suggest any treatment. According to this document high titer was defined as 5 million HCV RNA copies per ml. Table 1 indicated that patients infected with HCV genotypes 1, 2, and 5 have an average viral load greater than 2 million.

The technical problem to be solved could be defined as providing improvement for any specific cohort of patients without subjecting any other cohort that would not benefit to treatment. Claim 1 provided a solution to this problem, see Table 17 of the patent.

Document (OD104) was a post-published document and thus irrelevant to the assessment of inventive step. In any case, the document (cf. page 216, Figure 4) did not recommend to treat all HCV-1 infected patients with the combination but only those that were HCV-RNA negative at week 24. This corresponded to a tweaking of the paradigm with regard to genotype 1 patients depending on the results obtained after 24 weeks.

It was also not true that HCV-1 infected patients benefited in general from the prolonged combination treatment. There was a special technical effect, namely the threefold better response between 24 and 48 weeks of combination treatment for the claimed subgroup (see Tables 14 and 17 of the patent).

Document (OD2) alone could not render the claimed subject-matter obvious. Document (OD2) provided an invitation for a research program (see page 111S) and no results before the priority date. There was nothing

to indicate that the authors of document (OD2) had any hope to succeed or had a reasonable expectation of success. There was no information provided as to the genotype grouping of the patients being studied, their viral load, the dosage of ribavirin, the type of interferon or the dosage of interferon. The mere announcement in document (OD2) that clinical trials were under way did not make the results of these studies available to the public (see also decision T 715/03, point 2.2 on page 13, second paragraph and point 2.4.1 on page 14, first paragraph).

In particular, document (OD2) did not say to start from HCV-1 infected patients with a high viral load but aimed at improving the treatment in general - by looking at all patients. It was part of the inventive concept that only a particular subgroup benefited from the prolongation of the combination treatment. That subgroup had not been disclosed in document (OD2).

The combination of genotype 1 and viral load as predictors to response was not common general knowledge at the relevant date and was not disclosed in document (OD2) either. Document (OD3) provided evidence that viral load and HCV genotype were not considered in combination. The authors looked separately at viral load and genotype and found (cf. page 85, sentence bridging columns) that in the interferon-alpha 2b and ribavirin group, no baseline factor predicted a virological sustained response.

The authors of document (OD3) missed the connection with the response to combination therapy. None of documents (OD50), (OD110), (OD52), (OD53), (OD48),

(OD12), (OD46), and (OD83), relied on by appellant III to argue that the skilled person would have identified the claimed patient group, belonged to the common general knowledge or identified patients with HCV genotype 1 infection and a viral load greater than 2 million as an independent patient subgroup.

The property of being difficult to treat was not predictive of success. That genotype 2 or 3 infected patients and patients with a low viral load were easy to treat had nothing to do with whether it was predictable whether hard to treat patients would respond to prolonged therapy or not. The response to combination treatment was not predictable.

Document (OD50) did not mention a specific genotype or viral load in the second full paragraph on page 6S and there was no mention of a combination treatment period longer than 6 months. Moreover on page 8S the document recommended an initial treatment with interferon for 12 months. There was no indication in that document that interferon should be combined with ribavirin for any time period greater than 6 months.

Document (OD3) offered several possibilities (page 86, right hand column, last paragraph) to treat difficult to treat patients: higher dose, longer treatment course, new antiviral drugs. It was not logical to assume that especially hard to treat patients would respond better to longer treatment. The skilled person would expect them to continue not to respond. It was logical to assume that easy to treat patients would respond better to longer treatment.

The reasoning of decision T 531/04 could not be used by analogy to assess inventive step in the present case because the factual situation underlying the present case was different.

The skilled person was not in a "try and see" situation, see decisions T 847/07 (points 68 to 70) and T 293/07 (points 35 to 37). Clinical trials on humans were certainly not routine tests; the skilled person, who was extremely cautious, would therefore not adopt a "try and see" attitude.

The suggestion that predictions for response to IFN monotherapy were transferable to combination therapy was contradicted by the evidence on file. Document (OD2) taught (see page 110S, right column, last paragraph) that patients infected with HCV genotype 2 or 3 responded equally well to interferon alone and to combination treatment. However, from document (OD3) by the same authors as document (OD2) it could be seen (page 86, Table 4) that the combination therapy worked better than interferon monotherapy in genotype 2 and 3 infected patients. Table 17 of the patent confirmed what document (OD3) said: HCV genotype 2 and 3 infected patients benefited from combination therapy. The predictive suggestions in document (OD2) were thus not necessarily true. It followed that predictions from IFN monotherapy to combination therapy did not hold good.

This was further corroborated by document (OD1), see page 1311, right hand column, first paragraph and document (OD3), see page 83, right column, 5th paragraph and page 86, left column, last paragraph.

Document (OD60) explicitly stated, see last paragraph in the left column on page 705, that the results reported therein may not be transferable to other patient populations as a result of other risk factors.

Document (OD112) was an abstract that reported only on non-responder patients and did not provide SVR results.

The "expectations of the skilled person" summarised in document (OD113) were pure speculations made after the priority date.

According to document (OD123) it was impossible to predict accurately which patients will eliminate the virus if given interferon (see page 69). Document (OD123) did not mention any correlation of viral load to HCV genotype 1 and success of treatment.

According to document (OD52) pre-treatment HCV RNA levels were not a very reliable indicator of subsequent response to interferon therapy (see page S-72, left hand column, third paragraph).

Document (OD2) stated (abstract) that the optimal use and regimen of combination therapy awaited further investigation. Document (OD2), page 108S, right column also disclosed that "[t]he mode of action of ribavirin is not well understood". According to document (OD123) very little was known about how ribavirin worked and what it did (see page 81, first full paragraph).

Claim 1 was inventive over the disclosure in the paragraph in the left hand column on page 111S of document (OD2). The invention considered viral load and

HCV genotype in combination and the patent provided a direct comparison of IFN monotherapy and combination therapy at 24 and 48 weeks. Document (OD2) proposed monotherapy and combination therapy for 24 weeks and 48 weeks and it did not disclose the HCV genotype in combination with the viral load.

- XIX. The submissions by appellant II (opponent 02), insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of document (D128)

If document (D128) was filed to clarify the teaching of document (OD12) there was no excuse for not submitting it earlier, as document (OD12) was filed with the notice of opposition. This document was not more relevant than any document in the proceedings.

Admissibility of document (D129)

This document had not been filed earlier because it had only been found recently. It was more relevant than document (OD8) because it described the successful treatment of chronic hepatitis C in interferon-naïve patients by administering the combination of interferon and ribavirin for a 12 month period. The only features missing were genotype 1 and viral load, but 50% of all HCV infected patients had these features anyway.

Binding effect of decision T 1399/04

The interpretation of the sentence bridging pages 110S and 111S in document (OD2) adopted by the board in

decision T 1399/04 was not *res judicata*. Decision T 1399/04 related to novelty only and was not binding on the present board when considering inventive step.

Interpretation of claim 1

In the light of paragraph [0025] of the patent any patient with one or more of the listed signs fell within the scope of claim 1. The patients of document (OD12) had several of those signs and therefore fell within the ambit of the claim.

Claim 1 did not require a sustained viral response but related to eradication immediately after 40 to 50 weeks at the end of treatment.

Inventive step

In the written phase of the appeal proceedings appellant II relied on document (OD2) as closest prior art and defined the problem to be solved as for how long to treat the patient group disclosed in document (OD2), see the paragraph bridging pages 110S and 111S. As acknowledged in the declaratory evidence in the proceedings, i.e. documents (OD106), (OD107) and (OD108), the skilled person would have expected high viral load, HCV genotype-1 infected patients to benefit from a prolonged therapy by virtue of being known to be "difficult to treat". As each expert has stated, he would be optimistic of seeing an improvement in this patient group after an extended therapeutic regime to the extent that a threefold improvement would not be inconsistent with what had previously been observed with interferon monotherapy in document (OD60).

Document (OD107) also points to document (OD33) as providing this specific guidance for high viral load, HCV genotype-1 infected patients. The experts have drawn further support for their position from documents (OD112) and (OD113).

At the oral proceedings appellant II stated that its case was based on document (OD2), either alone or in combination with the common general knowledge as disclosed in document (OD121) on page 11 or in combination with document (OD50), see page 8S.

Document (OD2) represented the closest prior art. It disclosed (see page 108S) that the combination of ribavirin and interferon worked better than monotherapy with interferon for all patients and that it worked better in difficult to treat patients (page 109S, from left column bottom to right column, 2nd and 3rd paragraphs). Moreover it disclosed (see page 110S, right column) the exact patient group of claim 1 because the sentence bridging pages 110S and 111S, when read together with the previous sentence, did disclose a patient having a high HCV RNA level and genotype 1 HCV infection. Even if document (OD2) was considered not to disclose the patient group - this did not matter as 50% of all HCV infected patients with chronic hepatitis C were infected by HCV-1 and had a high viral load, see Table of document (OD80).

The subject-matter of claim 1 was obvious in view of three different lines of argumentation.

First, the technical problem to be solved was to provide an improved therapy regimen for patients with

chronic hepatitis C, who were interferon-naïve, infected with HCV-1 and had a high viral load. The solution, namely to extend the combination therapy from 6 months to 12 months was obvious over document (OD2) alone; over document (OD2) in combination with the common general knowledge; and over document (OD2) in combination with document (OD50).

Document (OD2) provided a clear pointer in the second full paragraph on page 111S to treat for 48 weeks. It was common general knowledge that 12 months was the standard duration for IFN monotherapy of the same patients at the priority date (see document (OD121) on page 11). That IFN monotherapy extended to 12 months worked better was also known at the priority date from document (OD50) on page 8S. In summary, there was a trend to increase to 12 months to see an improved result. There was also a reasonable expectation of success because otherwise the clinical trials would not have been permitted by the authorities (see document (OD116), paragraph 19).

Second, the inventive concept of the patent could be derived from Table 17 in the patent. Although the data in the patent supported this concept, the post-published document (OD104) reported that a more detailed analysis of the trials showed that all HCV-1 infected patients benefitted from combination therapy. According to document (OD104) all patients with HCV-1 infection should be treated for 1 year. Thus although the patent may have demonstrated an effect with regard to document (OD2), it was an arbitrary effect which did not provide a solution to the problem to be solved, i.e. the administration of the combination therapy to a

limited group of patients who will benefit most from the prolonged treatment.

Third, alternatively the disclosure in the paragraph in the left hand column on page 111S of document (OD2) could be taken to represent the closest prior art. If the distinguishing feature was considered to be the genotype of the HCV virus and the viral load, then the effect had to be shown for this patient group.

According to the patent (page 18, Table 14) only 28% of the claimed patient group benefited from 48 weeks combination therapy while other patient groups benefited more. Bearing in mind that documents (OD2) and (OD8) already disclosed the treatment for 48 weeks, no advantage in relation to the distinguishing feature had been shown. It followed that the patient group represented an arbitrary selection from the patient group as a whole. The problem had to be reformulated to the provision of an alternative patient group and the solution was obvious in the absence of any particular advantage associated with the claimed patient group.

Document (OD3) did not contradict what was said in document (OD2). Document (OD2) recommended monotherapy for patients with a low viral load and combination therapy for patients infected with HCV genotype 1 and a high viral load. Table 4 of document (OD3) reported EOT response (left half) and SVR (right half). For EOT response the results obtained with combination therapy and interferon monotherapy were the same. The patent was not directed to SVR but claimed eradication at the end of treatment. There was nothing in document (OD3) that contradicted the recommendation made in document (OD2), considering that one had to look at EOT

response.

It was of no relevance that there were no *in vitro* or animal models because the combination treatment was already used in clinical trials. Decision T 715/03 and all other decisions referred to by appellant I were not applicable because they related to the use of a known drug in a different disease. In the present case, neither the drug nor the disease were new. Document (OD2) disclosed the same disease as in the patent and that clinical trials were under way. There was nothing to plausibly contradict that the combination would not treat hepatitis C, in fact there was ample prior art that showed that the combination worked.

- XX. The submissions by appellant III (opponent 03), insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of document (D128)

It was contested that the proprietor needed document (D128) to support an argument that was already on file.

Admissibility of document (D129)

This document contained more data than the documents on file and was thus relevant.

Interpretation of claim 1

Claim 1 did not refer to chronic hepatitis C but to chronic hepatitis C infection for which paragraph [0025] of the patent provided a definition.

Chronic hepatitis C and chronic hepatitis C infection were not the same.

Inventive step

In the written part of the appeal proceedings appellant III relied on documents (OD1), (OD2), (OD8), (OD12), (OD43) and (OD60) as closest prior art and submitted that it was appropriate to repeat the problem solution approach taking possible alternative starting points. At the beginning of the oral proceedings it stated that its case was based on documents (OD2), (OD8), or (OD12) as closest prior art. During the course of the oral proceedings it also relied on document (OD19) or the common general knowledge as closest prior art.

Document (OD1) qualified as closest prior art. It disclosed the treatment of HCV genotype 1 infected patients having chronic hepatitis C with the combination of ribavirin and interferon and related thus to the same technical field.

Document (OD43) taught the use of ribavirin monotherapy for 48 weeks to treat chronic hepatitis C and also hinted at combining ribavirin and interferon-alpha. It could also be considered to represent the closest prior art.

Document (OD60) described three different treatment schedules A, B, C with interferon-alpha-2a in chronic hepatitis C. Hence, it related to the same technical field as the alleged invention.

The skilled person knew that HCV genotype 1 infected patients with chronic hepatitis C and high viral load were difficult to treat. This common general knowledge could be considered to represent the closest prior art.

Alternatively, document (OD2) could be considered to represent the closest prior art. It disclosed the combination therapy in the treatment of chronic hepatitis C patients (paragraph bridging 110S and 111S). As the group of patients claimed was not explicitly disclosed in document OD2 the objective technical problem to be solved in view of document (OD2) was to identify the patient group that profited most from an extension of the combination therapy from 24 to 48 weeks. The avoidance of side effects in untreated patient cohorts was not reflected in the claimed subject-matter and therefore should not be taken into account when determining the objective technical problem to be solved.

On the basis of document (OD104), see page 212, it was contested that the patients as defined in claim 1 profited most from the prolongation of the combination therapy. Hence the problem to be solved in view of document (OD2) should be reformulated to "identifying a patient group that profits".

The solution proposed in claim 1 lacked an inventive step over document (OD2) in view of five different lines of argumentation.

First, the solution was obvious from document (OD2) page 111S (last sentence of second full paragraph) which indicated that the aim of the clinical trials was

to provide recommendations and a basis for approaching the decision of whether to use combination therapy or interferon alone. Decision T 1399/04 (point 34) had considered that it was probable that the exact clinical set up of claims 1 to 3 would be covered in the clinical trials.

Following the standard approach taken in other studies would have revealed what was claimed now, see document (OD50) page 5S, right hand column, fourth paragraph and page 6S, right hand column, seventh paragraph; document (OD110) page 1051, left hand column, last paragraph; document (OD52) page S-72, right hand column; document (OD53) page 105S, sentence bridging columns; document (OD48) page 1351, right column, first full paragraph; page 1353, right column, first full paragraph, Figure 1; document (OD12) page 503, right column, third paragraph. That the viral load and the HCV genotype would have been looked at was also supported by document (OD46), see page 413, Table III; document (OD107), see page 1; document (OD83). It was not an inventive activity to break down study results into viral load and HCV genotype but common practice at the priority date. It was also common practice to look at the sustained response to evaluate the success of the treatment. Decision T 715/03 was not applicable to the present case.

Second, document (OD2) already indicated for whom combination treatment should be considered initially. There was a reasonable expectation of success that "difficult to treat" patients would benefit from extending the combination treatment to 48 weeks because the skilled person knew from document (OD50) on page

6S, left hand column, second full paragraph, that the combination of interferon alpha and ribavirin lead to higher virological sustained response rates than interferon alpha alone in 6 months clinical trials and also that it had shown promise in the re-treatment of patients who relapsed after interferon monotherapy. Document (OD30) disclosed that the proportion of sustained response in non-responders might be further increased by modification of dosage and duration of the combination.

Third, the skilled person knew that HCV-1 infection and high viral load went hand in hand and were known to be difficult to treat. These patients needed a more aggressive treatment and hence it was obvious to prolong the combination treatment to 48 weeks, considering that combination treatment for 24 weeks was known and that document (OD12) already disclosed the successful application of the combination treatment for two consecutive periods of 6 months each.

Fourth, the board had pointed out in decision T 531/04 (see point 32 of the reasons) relating to non-responder patients, relying on the passage on page 111S, left hand column, second full paragraph of document (OD2) that the situation was one where it was "obvious to try". As regards the reasonable expectation of success the observations made by the board in decision T 531/04 (see point 33 to 39 of the reasons) likewise applied to the interferon-naïve patients of the present case. The conclusion reached by the board in decision T 531/04 (see point 41), namely that the skilled person would have reasonably concluded that the sub-group of patients which would benefit most in terms of relative

rate of sustained virological response from extending treatment from 24 weeks to 48 weeks was likely to include the sub-cohort of non-responders having a genotype 1 HCV infection and a viral load of greater than 2 million copies/ml, was applicable to the interferon-naïve patients of the patent in suit.

Fifth, it could be argued that the person skilled in the art would at least have adopted a "try and see" attitude towards the use of interferon and ribavirin for treating naïve patients having an HCV genotype 1 infection and a viral load of greater than 2 million copies per ml of serum for a period of 40 to 50 weeks. In accordance with the case law of the board of appeals (see decisions T 1045/98, T 380/05) obviousness was then at hand.

The same arguments as in relation to document (OD2) could be made starting from document (OD19) as closest prior art.

Alternatively, document (OD8) could be considered to represent the closest prior art. It disclosed the use of ribavirin and interferon-alpha in the manufacture of a pharmaceutical composition for treating chronic HCV infections and thus related to a similar purpose. The document did not refer to a specific HCV genotype and did not mention the viral load of the patients. The patient group according to claim 1 differed from the patient group of document (OD8) by pathological (HCV, genotype 1) and physiological characteristic (viral load $> 2 \times 10^6$ copies/ml). Following decision T 1399/04 (point 35 of the reasons), the technical effect associated with the treatment regimen as compared to

document (OD8) was the provision of a treatment regimen defining the patient group which profited most therefrom. Hence, the objective technical problem to be solved in view of document (OD8) was to provide knowledge about which patients profited most from the combination therapy for 48 weeks.

In line with the impugned decision, document (OD12) could be considered to represent the closest prior art. It disclosed the use of the combination of interferon and ribavirin followed by ribavirin monotherapy (cf. page 502, left column, right column). The sole difference to claim 1 consisted in the presence of interferon for the entire treatment period. As no effect was linked to this difference the problem to be solved was the provision of an alternative treatment regime. The problem was solved by prolonging the interferon treatment to the standard 12 months duration. On the basis of paragraphs 16 and 19 of document (OD116) a reasonable expectation of success with regard to the particular patient group could be derived from the announcement of clinical trials in document (OD2).

XXI. The submissions by appellant IV (opponent 04), insofar as they are relevant to the present decision, may be summarized as follows:

Inventive step

Document (OD12) met the requirements for the closest prior art. It disclosed (cf. page 501, left column, "Treatment protocol", lines 1-4; right column, "Patient characteristics", line 6) the use of ribavirin in

association with interferon alpha for treating chronic hepatitis C infection. The disease the patients in document (OD12) were suffering from before transplantation was a chronic hepatitis C infection. After transplantation more than half of these patients developed recurrent HCV hepatitis (cf. page 501, right column, "Patient Characteristics", line 6). Thus, recurrent HCV hepatitis in this context meant chronic hepatitis C infection. The patients in document (OD12) showed elevated ALT levels, were positive for antibodies to HCV and for HCV-RNA, and their liver biopsies were compatible with active hepatitis (cf. page 501, left column, "Study Population", lines 3-12). In the opposed patent, these criteria were mentioned among those defining a person suffering from chronic hepatitis C infection (cf. paragraph [0025]). Document (OD12) further disclosed (cf. page 502, left column, last paragraph, lines 2-3) eradication of detectable HCV-RNA. The object underlying the subject-matter of claim 1 was to provide an effective therapy. The solution provided by the subject-matter of claim 1 was obvious in view of the teaching of document (OD59).

Requests

- XXII. Appellant I requests that the decision under appeal be set aside and that the patent be maintained as granted or on the basis of one of its auxiliary requests 1 to 8 filed with its statement of grounds of appeal. Appellants II-IV request that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Introduction

1. The invention relates to the treatment of chronic hepatitis C. The hepatitis C virus (HCV) is the most common cause of hepatitis C. At least six genotypes (HCV-1 through HCV-6) and more than 30 sub-genotypes of HCV had been identified by the priority date of the contested patent. While 15% of HCV-infected individuals clear the infection within 6 months, the remaining 85% develop chronic hepatitis C with persistent viremia. At the priority date, one way of treating chronic hepatitis C was by parenteral administration of interferon. The response to therapy was defined as either the "end of treatment" (EOT) response or as the "sustained response" (SR) 6 months or more after cessation of therapy and was based on biochemical (normalization of serum alanine aminotransferase (ALT) levels) or virological criteria (absence of detectable HCV RNA). Patients who had not been previously treated with interferon were considered "naïve" patients. It was also known that certain patients do not respond to initial treatment with interferon at all (so-called "non-responders") or responded initially to the treatment only to relapse later (so-called "relapsers").

Admissibility of documents (D128) and (D129) in the proceedings

2. Document (D128) was filed one month before the oral proceedings in reaction to a statement qualified as "*obiter dictum*" in the decision under appeal. Appellant I gave no reasons and none are apparent for not filing

- document (D128) with the statement setting out the grounds of appeal.
3. Document (D129) was filed three weeks before the oral proceedings as evidence in support of the ground for opposition (Article 100(a) EPC 1973 in conjunction with Article 56 EPC 1973) which was put forward in the notice of opposition. This document should thus have been filed within the opposition period or with the statement setting out the grounds of appeal at the latest. The argument that the document has been filed as soon as it came to the attention of appellant II can not distract from the fact that the document has not been filed at the appropriate point in time in the proceedings.
 4. The board therefore considers that both documents (D128) and (D129) have to be regarded as "late-filed" in the sense that they could or should have been filed earlier. Appellants II and III both consider document (D128) as no more relevant than any document in the proceedings and request not to admit document (D128) in the proceedings. Appellant I objects to document (D129) being admitted into the proceedings on the ground that it is irrelevant.
 5. Pursuant to both Article 114(2) EPC and Article 13 RPBA the admission of evidence not filed in due time is at the board's discretion. When assessing the admissibility of new evidence submitted at a late stage of the proceedings the relevance of the document is one of the criteria to be taken into account (see Case Law of the Boards of Appeal of the European Patent Office,

6th edition 2010, VII.C.1.2).

6. As regards document (D128), it relates to the course of hepatitis C virus infection after liver transplantation and corresponds to reference 2 of document (OD12). In the decision under appeal document (OD12) was considered to represent the closest prior art document because the opposition division considered that there was at least a partial overlap between the patients of document (OD12) and those of the claims. However, in the *obiter dictum* the opposition division expressed doubts as to whether the patients treated in document (OD12) had already developed chronic hepatitis C (see section IX above).
7. The question of whether the patients of document (OD12) who receive combination therapy after liver transplantation have chronic hepatitis C is of high relevance to the decision to be taken. Since document (D128) reports on the occurrence of HCV-related acute hepatitis and its progression to chronic active hepatitis after liver transplantation, the board decides to exercise its discretionary power in favour of admitting document (D128) into the appeal proceedings.
8. Document (D129) is comprised of several slides reporting on the combined use of interferon and ribavirin for the treatment of HCV. Slide 8 relied on by Appellant II discloses **estimated** sustained response rates for different drug regimes at 6 and 12 months. The estimation is made for patients that are either IFN-naïve, relapsers or non-responders. The HCV genotype or the viral load are not considered in the

estimation. No explanation is provided as to how the estimation was carried out.

9. In the board's view the provision of a mere estimation of a sustained response rate does not qualify as a disclosure of a successful treatment. This is especially so if the skilled reader is not informed which criteria were used to make the estimation. Thus, the argument of appellant II, that document (D129) was more relevant than document (OD8) as it described the successful treatment of chronic hepatitis C in interferon naïve patients by administering interferon-ribavirin combination therapy for a 12 month period, is unpersuasive. Therefore the board concludes that document (D129) is not *prima facie* more relevant than the prior art that has already been cited in the proceedings and decides not to admit document (D129) in the proceedings.

Main request

Binding effect of decision T 1399/04

10. As set out above in sections VII-X, the present case constitutes the second appeal concerning the patent and the only issue to be decided with regard to the main request is inventive step.
11. The parties disagree on whether the interpretation of document (OD2) by the board in decision T 1399/04 (*supra*, point 34 of the reasons, page 25, second paragraph) is binding on the present board or not. While appellant I considers that the finding is *res judicata* and binding, appellant II submits that the

relevant finding in the context of novelty is not *res judicata* and is not binding on the present board in its assessment of inventive step.

12. According to established jurisprudence, "*res judicata*" means a matter finally settled by a court of competent jurisdiction, rendering that matter conclusive as to the rights of the parties and their privies, such a final judgement constituting an absolute bar to a subsequent legal action involving the same claim, demand or cause of action, and the same parties or their privies (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, VII.E.11.1). It follows, that the following findings of the board of appeal in the first appeal proceedings (cf. decision T 1399/04, *supra*) are "*res judicata*" for the present appeal proceedings: the subject-matter of claims 1-11 as granted is entitled to the claimed priority, relates to patentable subject-matter, finds a basis in the application as originally filed, and is novel over the public prior use disclosed in document (OD105) and the disclosure of documents (OD2), (OD8) and (OD12). The interpretation of document (OD2) by the board in decision T 1399/04 (*supra*) is consequently not "*res judicata*".

13. However, for the interpretation of document (OD2) in the present appeal proceedings the provisions of Article 111(2) EPC are of relevance. Pursuant to Article 111(2) EPC, if the board of appeal remits the case for further prosecution to the department whose decision was appealed, that department shall be bound by the *ratio decidendi* of the board of appeal in so far

- as the facts are the same.
14. According to the established jurisprudence of the boards of appeal, the same binding effect applies to a subsequent appeal in respect of an earlier decision of a board of appeal as it applies to the department of first instance (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, VII.E.11.1). This has not changed with the introduction of new Article 112a EPC (Petition for review by the Enlarged Board of Appeal), see decision T 365/09 of 14 April 2010 (point 2 of the reasons). Accordingly, the board in the present appeal proceedings is bound by the *ratio decidendi* of earlier decision T 1399/04 (*supra*) in so far as the facts are the same.
15. It is well established that the "*ratio decidendi*" of a decision under Article 111(2) EPC is the ground or the reason for making it - in other words, the point in a case which determines the outcome of the judgement (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, VII.E.11.1). The ground or reasons for making the decision that the subject-matter of claim 1 is novel over document (OD2) is thus of relevance.
16. In decision T 1399/04 (*supra*) the board analyses document (OD2) and notes (see point 34 of the reasons, second paragraph on page 24):
- "In the chapter titled "Discussion" on page 110S, right column, it is said that it is difficult to recommend combination therapy as the first approach to treatment for interferon naïve patients. Especially patients with*

a favourable clinical profile (young age, low viral load or infection with HCV genotype 2 or 3) respond equally well to interferon alone. The sentence bridging pages 110S and 111S reads as follows:

*"In this respect, patients with high HCV RNA levels, genotype 1, high degrees of viral genomic diversity, **or** histological evidence of advanced fibrosis or cirrhosis would be candidates to receive combination therapy initially." (emphasis added by the board)."*

The board then explains how it understands the sentence bridging pages 110S and 111S of document (OD2), (see decision T 1399/04, *supra*, point 34 of the reasons, page 25, second paragraph):

*"The sentence bridging pages 110S and 111S (see above) lists several parameters of a clinical profile that would make an interferon naïve patient a candidate for receiving combination therapy initially. The first three of these parameters are separated by commas, the third and fourth parameters are separated by the word "**or**". The Board concludes that the authors of document (OD2) considered a patient having a high HCV RNA level, **or** genotype 1, **or** a high degree of viral genomic diversity, **or** histological evidence of advanced fibrosis or cirrhosis, to be a candidate for combination therapy."*

17. Hence there can be no doubt that one of the reasons for finding the subject-matter of claim 1 to be novel over document (OD2) was that this document did not disclose the patient group as defined in present claim 1 (see decision T 1399/04, *supra*, point 34 of the reasons,

first paragraph on page 25).

18. Accordingly, the argument of appellant II that the sentence bridging pages 110S and 111S of document (OD2), when read together with the previous sentence relating to patients with a favourable clinical profile, discloses a patient group having a high HCV-RNA level **and** genotype 1 runs contrary to the *ratio decidendi* in decision T 1399/04 (*supra*).

19. The board would not be bound by the *ratio decidendi* in decision T 1399/04 (*supra*) if the facts were not the same (see last sentence, point 14 above). However, document (OD2) has not changed nor have the claims under consideration. The question which needs to be answered is thus whether consideration of the sentence bridging pages 110S and 111S in document (OD2) in combination with the previous sentence amounts to a new fact.

20. According to decision T 860/93 of 29 December 1993 (see point 5.1 of the reasons of the decision) "*[i]t is a general principle of law that the proper interpretation of any document, and more specifically any part of a document, is to be derived by having regard to the document as a whole. That principle is expressed in Latin as: Ex praecedentibus et consequentibus optima fit interpretatio. (The best interpretation is that made from what precedes and what follows).*" Appellant II has not advanced any indication that this principle was not followed by the board in decision T 1399/04 (*supra*) when arriving at the interpretation of document (OD2). In fact, it can be taken from decision T 1399/04 (*supra*, point 34 of the reasons, second to fifth

paragraph on page 24) that the board took into account not only the preceding but also the following sentences of document (OD2) when it arrived at its interpretation of the sentence bridging pages 110S and 111S. The present board concludes that the facts are, thus, unchanged.

21. It follows that the argument of appellant II which runs contrary to the *ratio decidendi* of decision T 1399/04 (*supra*) must be disregarded in view of the binding effect of T 1399/04 (*supra*) in the present appeal proceedings pursuant to Article 111(2) EPC. For the purpose of the present decision the sentence bridging pages 110S and 111S of document (OD2) is thus understood as disclosing a patient having either a high HCV RNA level, or a HCV genotype 1 infection, or a high degree of viral genomic diversity, or histological evidence of advanced fibrosis or cirrhosis, to be a candidate for combination therapy.

Interpretation of claim 1

"to eradicate detectable HCV-RNA"

22. Appellant II submits that the term *"to eradicate detectable HCV-RNA"* in claim 1 has to be interpreted to mean "eradicate" immediately after 40 to 50 weeks because that is the "end of treatment" according to claim 1.
23. It is established jurisprudence of the boards of appeal that the skilled person should try to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of

the patent. Absent a definition of a particular term in the specification, terms should be given their normal meaning in the relevant art (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, II.B.5.1 and II.B.5.3.3).

24. It is common ground between the parties that the term "detectable HCV-RNA" is defined in paragraph [0028] of the patent, but that the term "to eradicate detectable HCV-RNA" is not defined in the specification of the patent.

25. Appellant I argues that the normal meaning of "to eradicate" is "to get rid of completely" and that it is common general knowledge that eradication of HCV can not be measured during or immediately after termination of antiviral treatment. It submits that the sustained viral response has to be determined to evaluate whether the patient has eradicated the virus.

26. No reasons are advanced by Appellant II as to why the point in time of assessment of the efficacy of the treatment according to claim 1 necessarily has to coincide with the point in time when the treatment ends, i.e. at 40 to 50 weeks. Appellant II has moreover not contested that it was common general knowledge that eradication of HCV could not be measured during or immediately after termination of antiviral treatment. Therefore appellant II's argument that the point in time at which eradication has to be measured is that of the end of treatment specified in claim 1 does not convince the board.

27. In the board's judgement the interpretation advanced by appellant II also contradicts the teaching of the patent. Indeed, the board notes that in the patent eradication of serum HCV-RNA is determined consistently at the end of the follow-up period, i.e. 24 weeks after termination of therapy (see e.g. paragraphs [0064], [0073], [0083], and [0087], and Tables 3 and 10). In contrast, when HCV-RNA serum levels are measured at the end of treatment (EOT), the patent indicates these levels merely as "negative" or "positive", but is silent about any "eradication" of the virus (see e.g. Table 3). Moreover, according to paragraph [0080] of the patent "[t]he primary efficacy objective is sustained virologic response as defined by the loss of detectable serum HCV-RNA (qPCR) measured at End of Follow-up (24 weeks following the end of treatment)".
28. Taking into account the principles of interpretation developed by the boards of appeal (see point 23 above) the board concludes that the term "to eradicate detectable HCV- RNA" in claim 1 is to be equated with eradication of detectable HCV-RNA 24 weeks after the end of treatment and hence with "sustained viral response". Appellant II's arguments, which are based on the supposition that the expression "to eradicate detectable HCV-RNA" in claim 1 relates to eradication of detectable HCV-RNA immediately at the end of treatment, thus fail.

"chronic hepatitis C infection"

29. Appellant III contends that there is a difference between "chronic hepatitis C infection" and "chronic hepatitis C", although without substantiating in what

the difference consists. The board notes that at the priority date the skilled person was aware of the fact that hepatitis C is a RNA virus which infects humans and is the most common cause of chronic hepatitis C (see e.g. document (OD5), page 8, left column, first paragraph after abstract). Therefore the board sees no reason to doubt that the two terms have the same meaning for the skilled person.

30. Moreover appellants' II, III and IV all argue that the term "chronic hepatitis C infection" in claim 1 has to be construed in the light of the definition provided in paragraph [0025] of the patent. Therefore, in their view, patients having merely one of the signs or symptoms listed in paragraph [0025] of the patent, e.g. an elevated ALT level, would fall within the scope of claim 1.
31. Paragraph [0025] of the specification of the patent reads as follows: "*A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms: (a) elevated ALT, (b) positive test for anti-HCV antibodies, (c) presence of HCV as demonstrated by a positive test for HCV-RNA, (d) clinical stigmata of chronic liver disease, (e) hepatocellular damage.*"
32. As pointed out earlier (see point 25 above) it is established jurisprudence of the boards of appeal that terms used in patent documents should be given their normal meaning in the relevant art, unless the description gives them a special meaning. The board notes that whenever the specification of the patent provides the definition of a particular term in the

context of the present invention it does so explicitly. Thus, e.g. paragraph [0027] of the patent provides a definition of the term "antiviral treatment naïve patients" in the context of the present invention.

33. The board is therefore satisfied that the disclosure in paragraph [0025] of the patent does not amount to a definition of the term "chronic hepatitis C infection" in the context of the present invention. On the contrary, it merely recites some of the signs or symptoms a person suffering from chronic hepatitis C infection may exhibit. The board concludes that the term "chronic hepatitis C infection" in claim 1 has to be given the meaning it usually has in the field of hepatitis C infection. The argument of appellants II to IV, that patients having merely one of the signs or symptoms listed in paragraph [0025] of the patent, e.g. an elevated ALT level like the patients of document (OD12), would therefore fall within the scope of claim 1, thus fails.

Inventive step

The closest prior art

34. For the assessment of inventive step the boards of appeal apply the "problem and solution approach" which, as a first step, requires the definition of the "closest prior art". The boards have repeatedly pointed out that the closest prior art for assessing inventive step is normally a prior art document disclosing 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 to arrive at the claimed invention. A further criterion for the selection of the most promising starting point is the similarity of technical problem (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, I.D.3.1).

35. From the patent as a whole (see in particular paragraphs [0001], [0004], and [0005]) it is understood that the purpose of the present invention is the improved use of the combination of ribavirin and interferon alpha for treating antiviral treatment naïve patients having chronic hepatitis C infection to eradicate detectable HCV-RNA.
36. In the course of the appeal proceedings the following documents (OD1), (OD2), (OD8), (OD12), (OD19), (OD43), (OD60) or, alternatively, the common general knowledge were put forward as representing the closest prior art.

Document (OD1)

37. Document (OD1) reports on the long-term efficacy of the 24 week treatment of chronic hepatitis C with the combination of ribavirin and interferon in comparison with interferon monotherapy. Patients were followed up for 2 years and assessed for complete response, i.e. normal serum alanine aminotransferase (ALT) level and undetectable serum HCV-RNA. This disclosure thus relates to a similar purpose as the invention. The authors note however (see paragraph bridging columns on page 1311) that genotype 1b did not seem to significantly alter the outcome to the combination therapy. Also the pre-treatment HCV-RNA titer,

acknowledged to be a very important predictor of response to interferon therapy in some studies, did not seem to significantly influence the sustained response to the combination therapy.

Document (OD2)

38. Document (OD2) is a review article on the therapy of hepatitis C with the combination of ribavirin with alpha interferon and was published around 8 months prior to the priority date of the present invention. From the analysis of the results of four pilot clinical studies and one randomized, double-blind, placebo-controlled study of interferon-naïve patients with combination therapy the authors conclude that combination therapy appears to be more effective than interferon alone in naïve patients in terms of sustained response (see page 109S, right column, first full paragraph and second paragraph). Nevertheless, the authors state in the "discussion" section of the paper that for interferon-naïve patients it is somewhat difficult to recommend combination therapy as the first approach to treatment (see page 110S, right column last paragraph). On page 111S (left column, second full paragraph) the authors note that several multicenter and multinational randomized controlled trials comparing interferon alone to the combination with ribavirin were under way. These studies would compare 24 and 48 weeks of therapy and include large enough samples of patients to evaluate whether the combination is helpful in patients with all genotypes, all levels of HCV RNA, and all histological stages of disease. The teaching of document (OD2) thus aims at the same

purpose as the invention.

Document (OD8)

39. Document (OD8), a patent application, discloses the use of alpha interferon in combination with ribavirin in the manufacture of a pharmaceutical composition for treating chronic hepatitis C infections (claims 1 to 3). The patients may be previously untreated (column 3, line 36), and the duration of the treatment is from 6 to 12 months (claim 11). Its aim is the treatment of chronic hepatitis C infection while avoiding side effects normally associated with ribavirin and alpha interferon (column 1, lines 32 to 38; claim 1). Document (OD8) proposes to accomplish this by reducing the dosage or dosage duration or both compared to the previous monotherapies (column 2, line 50 to column 3, line 15; column 3, lines 49 to 51).
40. As established previously (see T 1399/04, *supra*, point 35 of the reasons) document (OD8) differs from the subject-matter of claim 1 in that it does not refer to a specific HCV genotype and does not mention the virus load of the patients. Moreover, neither eradication of HCV-RNA nor sustained virological response is mentioned in document (OD8). The board concludes that document (OD8) is not directed to the same purpose as the present invention and also fails to disclose the most relevant technical features of the invention.

Document (OD12)

41. Document (OD12) reports the results of a pilot study of the combination of interferon alpha and ribavirin as

therapy for recurrent hepatitis C after liver transplantation. The treatment encompassed 6 months of combination therapy followed by 6 months of ribavirin monotherapy. After 6 months of combination therapy HCV-RNA was undetectable in 10 patients. During ribavirin monotherapy, 5 of the 10 patients became HCV-RNA serum positive again (see page 502, paragraph bridging columns). A biochemical relapse was observed in three patients. These three patients received a second course of combination therapy followed by maintenance ribavirin monotherapy. The second course of combination therapy was instituted 6 months after the first course (page 502, left column, first paragraph).

42. Document (OD12) was considered to represent the closest prior art in the decision under appeal. The opposition division considered that its disclosure differed from claim 1 only by the fact that in the second half of the regime ribavirin monotherapy was used instead of a combination therapy with interferon. In the *obiter dictum* the opposition division considered however that it would appear that the patients of document (OD12) had not yet developed chronic hepatitis C when combination treatment was started (see section IX above).

43. Document (OD12) discloses that over 50% of liver transplant patients develop chronic active hepatitis after two years (see page 500, right column, second paragraph) and refers in this context to reference 2 which is document (D128) in these proceedings. Document (D128) relates to the course of hepatitis C virus infection after liver transplantation and reports (page 1138, right column, last paragraph; Fig. 1) that acute

lobular hepatitis developed in transplant patients within a mean of 4 months after liver transplantation whereas the actuarial rate of progression to chronic active hepatitis was 50% 2 years after the onset of acute hepatitis (page 1141, paragraph bridging columns; Fig. 2).

44. According to document (OD12) the mean time between transplantation and initiation of treatment was 9 months with a range of 3 to 24 months (see page 501, right column, sixth paragraph). Considering the time required to develop chronic hepatitis C after onset of acute hepatitis following liver transplantation the board concludes that at the onset of treatment the majority of the patients of document (OD12) had not yet developed chronic hepatitis C but had acute hepatitis C.
45. In the board's judgement the argument that the patients of document (OD12) had chronic hepatitis C merely because they had some of the symptoms mentioned in paragraph [0025] of the patent fails because paragraph [0025] does not provide a definition of the feature "chronic hepatitis C" in the context of the present invention (see point 33 above).
46. The contention that "recurrent hepatitis" means "chronic hepatitis C" because the patients had chronic hepatitis before transplantation is likewise unpersuasive because it appears (see point 43 above) that after transplantation patients develop acute not chronic hepatitis. Moreover it is noted that also in the relevant technical field chronic hepatitis C and recurrent hepatitis C after transplantation are considered different diseases, see e.g. document (OD2),

on page 109S, left hand column, last paragraph to page 110S, left hand column, second paragraph.

47. The argument that document (OD12) discloses eradication of HCV because it discloses that, after 6 months of combination therapy, serum HCV-RNA was undetectable in 10 patients (see page 502, left column, last paragraph, lines 2-3) is not accepted by the board. First, 5 of these 10 patients became HCV-RNA serum-positive during the subsequent ribavirin monotherapy. This is a clear indication that in these patients the virus was not eradicated after 6 months of combination therapy. Second, there is no proof in document (OD12) that HCV is eradicated in the other five patients who remained HCV-RNA negative after the end of the combination treatment, as all patients reported were still receiving ribavirin on a compassionate use basis at the time of writing document (OD12). Since ribavirin is a known antiviral agent that suppresses viral replication, any result reporting patients who became "HCV-RNA negative" can only be considered as a preliminary indication, because there is no possibility of determining whether a patient has truly eradicated HCV from the serum until the selective pressure imposed by ribavirin against viral replication has been removed from the patient.
48. The board concludes that document (OD12) does not relate to the treatment of patients having chronic hepatitis C and fails to disclose eradication of HCV. The purpose of document (OD12) is thus not the same as that of the claimed invention.

Document (OD19)

49. The publication date of document (OD19) could not be ascertained from the document itself. No evidence was provided by appellants II-IV to establish that document (OD19) belonged to the state of the art. Therefore, document (OD19) cannot be considered to represent the closest prior art for this reason alone.

Document (OD43)

50. Document (OD43) reports on a randomized, double-blind, placebo-controlled study of ribavirin monotherapy of chronic hepatitis C patients for 48 weeks. The document discloses (page 902, right column, third and fourth full paragraphs) that ribavirin monotherapy was not associated with the elimination of serum HCV-RNA and was rarely associated with sustained improvement in serum ALT levels. The authors conclude that ribavirin is of limited use for the treatment of chronic hepatitis C when given as a single agent for a finite period and that continuous therapy would be needed to maintain the benefit of the treatment. Towards the end of the document the authors note that the combination of ribavirin and interferon alpha might be more attractive than ribavirin as therapy for chronic hepatitis C and propose to compare the combination therapy and interferon monotherapy in a randomized, controlled trial in naïve patients with chronic hepatitis C. The board concludes that document (OD43) thus aims at the same purpose as the present invention.

Document (OD60)

51. Document (OD60) reports (see abstract) on a randomised trial comparing three different regimes of alpha-2a-interferon for the treatment of chronic hepatitis C. Schedule A involved a 12 month treatment starting with 6 million units (MU) three times a week and decreasing the dose on the basis of serum ALT activities; schedule B involved a fixed dose of 3 MU three times a week for 12 months; and schedule C involved a fixed dose of 6 MU three times a week for 6 months. Multivariate analysis indicated that younger age, shorter disease duration and infection with HCV genotypes 2a and 3 were independent predictors of sustained response.
52. The board notes that document (OD60) is silent on a possible combination of interferon with ribavirin for the treatment of chronic hepatitis C. Therefore, this document does not relate to the same purpose as the present invention.

Common general knowledge

53. The starting point for the assessment of inventive step should be one which is at least "promising", in the sense that there is at least some probability of a skilled person arriving at the claimed invention. In the board's judgement the common general knowledge that HCV-1 infected patients with a high viral load are difficult to treat does not allow for an obvious development leading to the claimed invention.

Closest prior art: conclusion

54. To summarise, document (OD19) does not belong to the state of the art and the common general knowledge is not a promising starting point. When deciding which of the remaining documents qualifies as closest prior art it has to be remembered that the intended purpose of a disclosure is the primary selection criterion for choosing the closest prior art. As documents (OD8), (OD12) and (OD60) are not directed to the same or a similar purpose as the claimed invention they do not qualify as closest prior art documents. Only documents (OD1), (OD2) and (OD43) are directed to the same or a similar purpose.
55. Document (OD1) differs from the subject-matter of the claims of the patent in that the duration of the combination therapy is only 24 weeks and longer duration of the therapy is not envisaged. Also, document (OD1) identifies the very two features (HCV genotype and pre-treatment HCV-RNA titer) which characterise the patients of claim 1 as non-predictive for sustained response.
56. The board notes that document (OD43) is silent about the length of the proposed combination treatment as well as the HCV genotype and pre-treatment HCV-RNA titer of the patients to be treated. Document (OD43) therefore discloses less of the features of the claimed invention than document (OD2) which discloses that the trials will compare 24 and 48 weeks of combination therapy and will take into account the HCV genotypes, the viral load and the histological stages of disease.

57. The board concludes that document (OD2) not only discloses subject-matter conceived for the same purpose as the claimed invention but also has the most technical features in common. Therefore the board decides that document (OD2) represents the closest state of the art for the purpose of the assessment of inventive step of the subject-matter of claim 1.

Technical problem and solution

58. As its main line of argument appellant II asserts that the paragraph bridging pages 110S and 111S in document (OD2) has to be understood as disclosing patients having high HCV RNA levels **and** a genotype 1 HCV infection. As an alternative line of argument, appellant II submits that, even if that paragraph is understood as disclosing patients having either high HCV RNA levels or a HCV-1 infection, then in the light of the teaching of document (OD80) at least 50% of all HCV-1 infected patients have a high viral load anyway. In its view document (OD2) therefore highlights that the particular patient group referred to in the claims of the opposed patent would be a candidate to receive combination therapy initially and it defines the problem to be solved in light of document (OD2) as the provision of an improved therapy regimen for patients with chronic hepatitis C, who are naïve, are infected with HCV-1 and have a high viral load.
59. In the board's judgement appellant II's main line of argument fails because it has been established that the sentence bridging pages 110S and 111S in document (OD2) is to be understood as disclosing naïve patients with high HCV RNA levels **or** genotype 1 HCV infection as

candidates to receive combination therapy initially (see point 21 above). The alternative argument is not persuasive because according to document (OD80) the median HCV RNA titer of chronic HCV-1 patients is 3,4 million copies of HCV RNA per ml, while a high viral titer is defined in document (OD80) as 5 million copies of HCV RNA per ml. Accordingly, the majority of the HCV-1 infected patients of document (OD80) do not have a high HCV RNA titer if the definition of document (OD80) for high viral load is used. Document (OD2) itself does not provide a definition of what is to be considered as high HCV RNA levels. Nor has it been established that there was a commonly accepted definition of high viral load in the relevant field by the priority date. Thus, in the board's view the skilled person when combining the teaching of document (OD80) with the teaching of document (OD2) would not arrive at the conclusion that document (OD2) highlights HCV-1 infected patients having a high viral load as candidates to receive combination therapy initially.

60. Hence, the problem as formulated by appellant II - which is based on the assumption that the patient group characterised as being infected with HCV-1 and having a high viral load is either disclosed or highlighted in document (OD2) - is inappropriate and can not form the basis on which inventive step is determined. The board concludes therefore that appellant II's main line of reasoning as to why claim 1 lacks an inventive step fails.

61. In the board's judgement starting from document (OD2) the problem to be solved by the claimed invention may be formulated as the identification of that patient

- sub-group among all antiviral treatment naïve patients having chronic HCV infection that profits most from prolonged treatment with the combination of IFN and ribavirin. Inclusion of the feature "and prevention of the treatment of patient cohorts that do not benefit" into the problem is not considered appropriate as this feature is not reflected in the claimed subject-matter.
62. As a solution to this problem claim 1 proposes to treat patients that are antiviral treatment naïve, have a HCV genotype type 1 infection and a viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR, for a time period of 40 to 50 weeks.
63. In view of the results reported in the patent (see Tables 6, 14, 16, and 17 of the patent) the board is satisfied that the patient group according to claim 1 profits most from an extension of the combination therapy from 24 weeks to 48 weeks and hence that the problem is solved by the subject-matter of claim 1.
64. Appellant II acknowledges that the data reported in the patent (cf. Table 17) support the inventive concept of the claims, but asserts that it has been found later that all HCV-1 infected patients benefit from combination therapy for 48 weeks, see document (OD104), on page 215, right hand column first full paragraph and on page 217, left hand column, last full paragraph. In its view claim 1 therefore does not provide a solution to the problem to be solved. According to appellant III the problem as defined in point 63 above is not solved by the claimed invention in light of the teaching of document (OD104) on page 212, left hand column, first

paragraph, and should be reformulated to "the identification of a patient sub-group that profits from combination therapy for 48 weeks".

65. Neither argument convinces the board. Article 56 EPC 1973 requires that the assessment of inventive step is made having regard to the state of the art. According to established jurisprudence of the boards of appeal the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person (see decision T 1329/04 of 28 June 2005, point 12 of the reasons; decision T 609/02 of 27 October 2004, point 8 of the reasons).
66. In the present case, appellants II and III rely on a post-published document to question whether the patent indeed solves the problem it purports to solve.
67. The first question which needs to be answered is thus whether post-published document (OD104) can be taken into consideration at all when assessing inventive step. According to established case law (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, I.D.4.6) post-published documents can be taken into consideration to confirm (or not) whether what appears to be a **plausible** solution at the relevant date is indeed a solution and hence whether the claimed subject-matter indeed solves the problem it purports to solve.
68. In the present case, the question of whether or not the solution is plausible at the relevant date does however

not arise. The patent contains the results from two clinical studies involving 912 and 832 patients, respectively, see paragraphs [0037] to [0101]. The data provided in Tables 6, 14, 16 and 17 show convincingly that patients according to claim 1 profit most from the prolongation of the combination therapy. Appellants II and III have not criticised or questioned these data. In fact appellant II acknowledged that the data in the patent in suit support the inventive concept. In the board's view there is accordingly no justification for considering post-published document (OD104) when deciding whether or not the problem is solved.

69. Moreover, in the board's judgement document (OD104) does not support appellant II's and III's arguments. Document (OD104) in fact does not recommend to treat all patients infected with HCV-1 for 48 weeks. Rather it recommends to treat all naïve patients with the combination of interferon and ribavirin for 24 weeks, to test the response to the treatment at this point and to base the decision to continue the treatment for a total of 48 weeks *inter alia* on the number of favourable factors (see page 217, left hand column, last paragraph to right hand column, second paragraph).
70. It is correct that document (OD104) also discloses (see page 215, right hand column, first full paragraph) that "*[t]he recommendation to treat patients with genotype 1 for only 24 weeks if the level of viremia is low is inadequate because we observed in this population 53% of sustained response versus 71% when treated for 48 weeks*". Corresponding statements are found on page 212, left hand column, first paragraph and on page 217 (see

left hand column, last full paragraph).

71. However, in the board's view these statements are not relevant to the subject-matter of claim 1 under consideration. Indeed, the board notes in this context that the classification of viral load into high or low in document (OD104) was based on the median, which was 3.5 million copies (see page 215, right hand column, fourth paragraph and Figure 4) whereas in the patent the patients were classified according to the number of HCV viral copies as having ≤ 2 million or ≥ 2 million copies per ml of serum. Hence, the population of patients with genotype 1 HCV infection and low viremia according to document (OD104) does not correspond to the patient population having genotype 1 HCV infection and a viral load ≤ 2 million copies per ml of serum according to the patent. The board concludes that the further analysis carried out in document (OD104) can not deter from the fact that the data reported in the patent showed an effect for patients infected with HCV-1 and a viral load ≥ 2 million per ml of serum.
72. As an alternative line of argument, appellant II submits that the patent fails to show an effect for the only two features (HCV genotype and the viral load of the patient) that distinguish the subject-matter of claim 1 from the trials disclosed in document (OD2) on page 111S, left hand column, second full paragraph. It argues that according to the patent (see Table 14 on page 18) only 28% of the patients according to claim 1 benefit from 48 weeks combination therapy whereas other patient groups benefit more. In its view the patient sub-group according to claim 1 therefore represents an arbitrary selection from the patient group as a whole

and the problem has to be reformulated to be the provision of an alternative patient group that can be treated with the combination therapy to which the solution is considered obvious in the absence of any particular advantage in relation to the distinguishing features.

73. In the board's judgement this argument does not hold good because document (OD2) does not in fact disclose to treat all naïve chronic hepatitis C patients for 48 weeks with the combination therapy but states that 24 weeks and 48 weeks of interferon monotherapy and combination therapy will be compared to evaluate whether the combination is helpful in patients with all genotypes, all levels of HCV RNA, and all histological stages of disease, see page 111S, left hand column, second full paragraph. Hence, not only the HCV genotype and the viral load, but also the duration of the therapy according to claim 1 must be taken into account when assessing inventive step vis-à-vis the teaching of this paragraph of document (OD2).
74. It is correct that according to Table 14 of the patent patients who received combination therapy for 48 weeks with genotypes other than HCV-1 and initial HCV levels of ≤ 2 million copies/ml achieved the highest sustained virologic response rates. However, only patients infected with HCV-1 and HCV-RNA levels ≥ 2 million copies/ml achieved sustained virologic response rates with 48 weeks of combination therapy that were 3 times higher than the rates achieved with only 24 weeks of the combination. This patient group thus benefits indeed most from an increased treatment duration and no

reformulation of the problem is needed.

Obviousness

75. As a first line of argument, appellant III submits that (i) the patient group of claim 1 would have been covered by the clinical trials mentioned in document (OD2), and that (ii) the skilled person following the standard approach taken in other studies would have necessarily determined the viral load and the HCV genotype of the patients and therefore arrived at the claimed subject-matter.
76. The first limb of the argument is based on decision T 1399/04 (*supra*, point 34 on page 25, last paragraph) which found that it was "*probable but in no case sure*" that the exact clinical set up of claims 1 to 3 will be covered by the clinical trials mentioned in document (OD2).
77. The board notes that the results of the clinical studies are not disclosed in document (OD2). Nor is there any evidence before the board that the results of the 48 weeks clinical trials mentioned in document (OD2) were available to the public at the priority date of the patent. From the mere disclosure in document (OD2) that clinical trials are under way the skilled person cannot draw any conclusions as regards any beneficial effect of the combination treatment for 48 weeks for any particular patient group, even if that patient group is included in the trials. This is so because the effect of the combination treatment on the eradication of the HCV-RNA in any patient group could only be evaluated after the treatment has been completed and

- the follow-up period lapsed so that the SVR analysis could be performed. That the combination of ribavirin and interferon was known in principle to have an effect in the treatment of hepatitis C is irrelevant in this context.
78. Appellant III based the second limb of its argument on the teaching of documents (OD50), (OD110), (OD52), (OD53), (OD48), (OD12), (OD46), and (OD83). It submits that these documents provide evidence that it was common practice in clinical trials to determine viral load and HCV genotype. Hence, it asserts, the skilled person in carrying out the clinical trials mentioned in document (OD2) and following the standard approach taken in other clinical studies would have arrived necessarily at the patient group according to claim 1.
79. In the board's judgment the documents relied on by appellant III do not support its conclusions as they merely indicate that viral load and HCV genotype are separate indicators for response to treatment with interferon.
80. In this context the board notes moreover that document (OD3) provides direct evidence that contradicts the assertion made by appellant III. In fact, it is derivable from document (OD3), see Table 4, that although the authors determined viral load and genotype of the patients they did not consider these parameters in combination, in other words they did not assess patients with genotype 1 HCV infection **and** high viral load as a distinct patient group. As a consequence, the authors of document (OD3) failed to find any correlation of sustained viral response with viral load

or HCV genotype (see page 85, paragraph bridging the columns) for the combination treatment. Also in document (OD1) the authors assessed HCV genotype and pre-treatment HCV RNA titer separately (see Table 1) and failed to find any correlation of the response to combination therapy with either (paragraph bridging columns on page 1311).

81. The board therefore concludes that although it is probable that the exact clinical set up of claim 1 will be covered by the clinical trials mentioned in document (OD2), appellant III failed to establish that the results of the 48 weeks trials were available to the public by the priority date of the opposed patent or that the skilled person would have identified any patient group, let alone a patient group falling within the scope of claim 1, as benefitting from the prolongation of the combination therapy by applying routine methods.

82. As a second line of argument appellant III submits that document (OD2) already indicates for whom combination treatment should be considered initially and that there was a reasonable expectation of success that "difficult to treat" patients would benefit from extending the combination treatment to 48 weeks in view of the teaching of documents (OD50) and (OD30).

83. In the board's judgement, appellant III's argument is not convincing because neither document (OD50) nor document (OD30) provide any indication that the property of being "difficult to treat" would be predictive of response to prolonged combination therapy. In fact document (OD50) merely states on page 6S, right

hand column, sixth full paragraph that "[a]lthough high HCV RNA levels **or** genotype 1 predict a less favourable response to therapy, treatment should not be withheld on the basis of these parameters." (emphasis by the board). Moreover, although document (OD50) discloses on page 6S, left hand column, second full paragraph, that the combination of interferon alpha and ribavirin leads to higher virological sustained response rates than interferon alone in 6 months clinical trials and also that it has shown promise in the re-treatment of patients who relapsed after monotherapy, document (OD50) itself does not disclose or suggest to increase the treatment with the combination beyond 6 months for any patient group. On the contrary, document (OD50) recommends, see page 8S, right hand column, first paragraph, an initial treatment with interferon alone - and not the combination of interferon with ribavirin - for 12 months and for all patient groups. Indeed it is specified that therapy should not be limited by mode of acquisition, risk group, HIV status, HCV RNA level, or HCV genotype. Also document (OD30) does not disclose that longer combination treatment will be successful in non-responders, but merely speculates that the sustained response might be increased by modification of dosage and duration of the combination.

84. The board observes in this context that the notion that "difficult to treat" would be predictive of sustained response to longer combination treatment is moreover contradicted by the prior art. Thus, document (OD3) reports on a randomised, double-blind, placebo-controlled trial of interferon α -2b with and without ribavirin for chronic hepatitis C. Although the authors of document (OD3) did see an improvement in the

virological sustained response after 6 months they conclude (see page 86, right hand column, last paragraph) that "[t]here are, however, many patients who do not respond to combination treatment [for 6 months]. Whether these patients will respond to higher doses or longer treatment courses and whether such schedules can be tolerated needs to be established. Finally, new antiviral drugs, such as the protease inhibitors, should be developed and evaluated for the treatment of chronic hepatitis C." Longer treatment was thus not the - and certainly not the only - answer to poor response after 6 months of therapy.

85. The board sees therefore no reasons to accept the proposition that the observation that treatment with the combination of interferon alpha and ribavirin for 6 months leads to higher virological sustained response in some patients in combination with the knowledge that certain patients were more difficult to treat would lead the skilled person to logically conclude that these patients would necessarily or at least most likely benefit from longer treatment with the combination of interferon and ribavirin.
86. As a third line of argument appellant III asserts that the skilled person knew that HCV-1 infection and high viral load go hand in hand and were difficult to treat. Therefore these patients needed a more aggressive treatment and it was obvious to prolong the combination treatment to 48 weeks, considering that combination treatment for 24 weeks was known and that document (OD12) already disclosed the successful application of the combination treatment for two consecutive periods of 6 months each.

87. In the board's judgement this argument fails for several reasons. First, document (OD2) states on page 111S, left hand column, second full paragraph, that "[t]hese studies will compare 24 and 48 weeks of therapy and will include large enough samples of patients to evaluate whether the combination is helpful in patients with all genotypes, all levels of HCV RNA and all histological stages of diseases". This statement confirms that it was not obvious that a particular patient group would benefit most from extending the combination treatment to 48 weeks at all and even less obvious that it would be a patient group falling within the scope of claim 1 in particular.
88. Second, prolongation of combination therapy to 48 weeks was not the only option the skilled person had when faced with the problem of trying to improve the treatment of chronic hepatitis C patients, see point 84 above.
89. Third, as regards document (OD12) it is noted that it has been established that this document is not concerned with the treatment of chronic hepatitis C in naïve patients but with the treatment of recurrent hepatitis C after liver transplantation (see point 44 above). Therefore the person skilled in the art has no incentive to consult document (OD12) in order to find a solution to the problem to be solved. Even assuming, for the benefit of appellant III's argument, that the skilled person would consider document (OD12), he would not envisage the claimed treatment regime because document (OD12) discloses combination treatment for 6 months followed by ribavirin monotherapy for at least 6

months followed by another 6 months of combination therapy followed by maintenance therapy with ribavirin alone.

90. A fourth line of argument pursued by appellant III is based on decision T 531/04 of 18 November 2005. In this decision the inventive step of a claim relating to the combination treatment of patients that failed to respond to a previous course of interferon-alpha monotherapy was denied. Appellant III asserts that the reasoning of decision T 531/04 would also be applicable to the opposed patent.

91. The board notes that in decision T 531/04 (*supra*) the closest prior art document D55 was considered to provide the skilled person with a specific patient group characterised by viral load and viral genotype and to describe a concrete study in which results were already reported. In the present case the closest prior art document (OD2) neither describes a concrete study nor does it disclose the exact patient group or any specific viral load within this group. Moreover document D22, which was relied on by the board in decision T 531/04 (*supra*) to establish that there was a common belief that a more aggressive (e.g. longer) treatment mainly turned further difficult to treat patients into responders, is document (OD17) in this appeal proceedings. As it was published after the priority date of the opposed patent it does not belong to the state of the art in the present proceedings. Moreover, in the present case it has been established (see points 83-85 above) that the prior art provided no indication for a common belief that a longer treatment would mainly turn difficult to treat patients into

- responders. In the board's judgement the reasoning of decision T 531/04 (*supra*) cannot therefore be used by analogy to deny inventive step in the present case.
92. As a fifth line of argument appellant III asserts that the skilled person would have at least adopted a "try and see" attitude towards the use of interferon and ribavirin for treating naïve patients having an HCV 1 genotype infection, a viral load of greater than 2 million copies per ml of serum for a period of 40 to 50 weeks and hence an inventive step was not present.
93. In decision T 1599/06 of 13 September 2007 (see point 20.2 of the reasons) the board observed that the "try and see" approach has been applied in the assessment of inventive step in situations where, in view of the prior art, the skilled person had clearly envisaged a group of compounds or a compound and then could determine by routine tests whether or not such compound(s) had the desired effect. In decision T 293/07 of 24 July 2008 the board considered (see point 37 of the reasons) that the testing of humans could not be considered to represent known routine tests and accordingly the skilled person was not in a "try and see" situation. Also in decision T 847/07 of 13 January 2001 (see point 70 of the reasons) the board considered it questionable whether the skilled person would adopt a "try and see" attitude at all in cases where human testing would be necessary in order to determine whether or not a compound has a certain property.
94. In the present case, it can be taken from document (OD2) that neither cell culture nor animal models of HCV were

available one year before the priority date of the patent. In fact document (OD2) states (see page 108S, right hand column, at the end of the first paragraph) that "*[u]nfortunately, cell culture systems and animal models of HCV replication are yet to be developed and the lack of simple in vitro and in vivo systems for evaluating antiviral agents for effects on HCV replication makes it necessary to investigate agents of promise in humans with this disease.*" No evidence is before the board that at the priority date this situation had changed. It follows that the effect of the combination had to be tested in humans. In line with established case law (see point 93 above) the board concludes that the skilled person was not in a "try and see" situation.

95. As yet a further line of argument, appellant II submits that document (OD2) discloses on page 110S, right hand column, last paragraph to page 111S, left hand column, first paragraph, the "difficult to treat" patient group as a candidate to receive combination treatment initially. It asserts that it would have been obvious to treat this patient group with the combination of interferon alpha and ribavirin for 12 months with a reasonable expectation of success on the basis of results obtained with interferon monotherapy in an equivalent patient group. In appellant II's view this proposition is corroborated by documents (OD106), (OD107), (OD108), (OD112), (OD113), and (OD33).

96. Documents (OD106), (OD107), and (OD108) are expert declarations drawn up after the priority date of the opposed patent. All three experts consider that the skilled person would have expected high viral load

- HCV-1 infected patients to benefit from prolonged therapy by the very virtue of being known to be "difficult to treat" and on the basis of results obtained in interferon monotherapy, in particular results obtained in document (OD60).
97. According to established jurisprudence of the boards of appeal (see decision T 296/93 OJ EPO 1995, 627, point 7.4.4 of the reasons), a "reasonable expectation of success" implies the ability of the skilled person to reasonably predict, on the basis of existing knowledge before starting a research project, a successful conclusion to said project within acceptable time limits. Therefore in the board's judgement the relevant question which needs to be addressed is whether the skilled person could have reasonably predicted, at the priority date, that the results obtained with interferon monotherapy were transferable to the combination therapy.
98. In that context documents (OD1) and (OD3) are of relevance. In document (OD1), see paragraph bridging columns on page 1311, the authors found that the pre-treatment HCV RNA titer, a very important predictor of response to interferon in some studies, did not seem to significantly influence the sustained response to the combination therapy. Document (OD3) provides evidence that predictions which are based on results obtained with IFN monotherapy were not necessarily transferable to the combination treatment. Thus, while HCV genotypes and baseline viral loads had both been thought to be useful in predicting a sustained treatment response to interferon-alpha-2b monotherapy (see page 86, left column, last paragraph) neither of these parameters was

found to predict a virological sustained response in the interferon-alpha-2b and ribavirin group (see paragraph bridging columns on page 85). And while document (OD2) recommends to treat patients with a favourable clinical profile - young age, low viral load, or infection with HCV genotypes 2 or 3 - with interferon alone because these patients seem to respond equally well to combination therapy and to interferon monotherapy (see page 110S, right hand column, last paragraph), document (OD3) provides evidence that patients infected with HCV genotypes 2 or 3a respond better to the combination therapy for 24 weeks than to interferon monotherapy (see table 4, sustained response).

99. The board also notes that the authors of document (OD60) warn the skilled person (see page 705, left column, last paragraph) that the results obtained with the more aggressive interferon monotherapy schedule, i.e. higher dose and longer treatment "*[m]ay not be transferable to other patient populations because the response to IFN- α is influenced by the age of the patient and by the duration of the disease, as shown in our study by multivariate analysis, and possibly also by presence or absence of cirrhosis.*"
100. In this context it is also of relevance that Professor Foster, the author of declaration (OD106) stated in document (OD123) shortly before the priority date of the contested patent, see page 69, first paragraph, that "*[i]t is impossible to predict accurately who will eliminate the virus if given interferon, although there is a broad distinction in current use between good and poor responders. Good responders are those with mild*

disease and no cirrhosis; bad responders tend to be older and have cirrhosis." As regards the combination treatment, document (OD123) states (see page 81, first full paragraph) that "[t]he dilemma facing anyone offered ribavirin as part of a combination therapy is that medical science knows very little about how it works and what it does. By taking it you enter uncharted waters where there may be hidden dangers."

101. The board concludes that at the priority date not even the response to IFN monotherapy was predictable. There were at least five independent predictors of poor response to interferon monotherapy: HCV genotype 1, high viral load, higher age, advanced fibrosis/cirrhosis, and genetic diversity of the virus which were all considered to have an effect on the outcome of the treatment of hepatitis C, see document (OD2), paragraph bridging pages 110S and 111S, document (OD50) page 5S, right hand column, third full paragraph; document (OD52), page S-72, left hand column, at the end of the second full paragraph, document (OD60), page 705, left column, last paragraph. According to document (OD52) liver histology was even the major factor which determined responsiveness to interferon therapy. And while HCV genotype showed some correlation, pre-treatment RNA levels were not considered to be a reliable indicator of subsequent response to interferon therapy at all (page S-72, left hand column, second full paragraph). Moreover, the mode of action of ribavirin was not well understood, see document (OD2), page 108S, right hand column, lines 15 to 23, and document (OD123) page 81, first full paragraph. Consequently there was also a lack of understanding as to how the combination of interferon-alpha and

ribavirin worked. Nor was it possible to reasonably predict which combination of the various factors known to play a role in interferon response would determine the response to treatment with the combination of interferon and ribavirin. Thus, in the board's judgement the skilled person had no incentive, based on the results obtained in interferon monotherapy, to extend the combination therapy to 12 months for any particular patient group with a reasonable expectation of success.

102. Documents (OD33), (OD112) and (OD113) are not considered to support appellant II's case either. Document (OD33) states (see document (OD33a), page 3, fourth paragraph) that for naïve patients with a high virus titer with or without cirrhosis and perhaps also a verified HCV genotype 1b infection, it should be considered whether to give combination treatment immediately, but document (OD33) is silent about the duration of the combination therapy. Document (OD112) relates to a one year combination treatment of non-responders, but reports data only for 24 weeks of treatment and is silent about any SVR. Finally, aside from the fact that the skilled person was not aware of document (OD113), an abstract, at the effective date of the opposed patent as it was published after the priority date of the opposed patent, the statement in document (OD113) relied on by appellant III is explicitly indicated to be a speculation (see document (OD113), last paragraph).

103. As a result, the board finds that neither document (OD2) alone nor its combination with the common general knowledge or any other prior art document would have

motivated the skilled person faced with the problem of identifying that patient sub-group, among all antiviral treatment naïve patients having chronic HCV infection that profits most from prolonged treatment with the combination of IFN and ribavirin, to arrive at a solution falling within the scope of claim 1 with a reasonable expectation of success. Since in the present case the selection of document (OD2) as the closest prior art document is clear beyond doubt it is not necessary to repeat the problem solution approach with any other document. The subject-matter of claim 1 involves an inventive step.

104. The above considerations in respect of claim 1 of the main request, i.e. the claims as granted, apply *mutatis mutandis*, to the subject-matter of independent claims 2 and 3 (see section II above) and to remaining claims 4 to 11 which are all dependent on claims 1 to 3. The main request fulfils the requirements of Article 56 EPC 1973.

105. In view of the decision on the main request, there is no need to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent as granted.

The Registrar:

The Chairman:

P. Cremona

C. Rennie-Smith