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# Datasheet for the interlocutory decision of 16 February 2023

**Case Number:** T 2643/16 - 3.3.07

**Application Number:** 08732818.3

**Publication Number:** 2203462

**IPC:** A61K31/7064, A61K31/7076

**Language of the proceedings:** EN

**Title of invention:**
NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

**Patent Proprietor:**
Gilead Pharmasset LLC

**Opponents:**
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Pharmaceutical Works POLPHARMA
Generics [UK] Ltd (trading as Mylan)
Teva Pharmaceutical Industries Ltd.
I P S Intellectual Property Services
STADA Arzneimittel AG
ZBM Patents - Zea, Barlocci & Markvardsen
Actavis Group PTC ehf

**Headword:**
Sofosbuvir/GILEAD

**Relevant legal provisions:**
EPC Art. 100(c), 87, 56

**Keyword:**
Added subject-matter - disclosure of individual diastereomers (no)
Inventive step - ex post facto analysis

**Decisions cited:**
G 0001/16, T 0658/91

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

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**Case Number: T 2643/16 - 3.3.07**

# I N T E R L O C U T O R Y  D E C I S I O N
## of Technical Board of Appeal 3.3.07
## of 16 February 2023

| | |
|---|---|
| **Appellant:** (Patent Proprietor) | Gilead Pharmasset LLC<br>Gilead Sciences, Inc.<br>333 Lakeside Drive<br>Foster City, CA 94404 (US) |
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| **Party as of right:**<br>(Opponent 9) | ZBM Patents - Zea, Barlocci & Markvardsen (OP9)<br>Rambla Catalunya, 123<br>08088 Barcelona (ES) |
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| **Decision under appeal:** | **Interlocutory decision of the Opposition Division of the European Patent Office posted on 31 October 2016 concerning maintenance of the European Patent No. 2203462 in amended form** |

**Composition of the Board:**

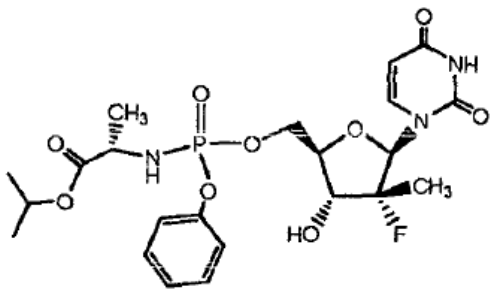
| | |
|---|---|
| **Chairman** | P. de Heij |
| **Members:** | J. Molina de Alba |
| | S. Albrecht |
| | E. Duval |
| | M. Blasi |

## Summary of Facts and Submissions

I. The decision under appeal is the opposition division's interlocutory decision rejecting the patent proprietor's main request (patent as granted) and finding that European patent No. 2 203 462 as amended in the form of auxiliary request 1 met the requirements of the EPC.

II. The patent had been granted with six claims. Claim 1 as granted reads as follows:

"*1. A compound represented by the formula*



"

This compound is commonly known as sofosbuvir.

Claim 2 is directed to the diastereomer of the compound of claim 1 having (S)-configuration at the phosphorous atom.

Claim 3 is directed to the diastereomer of the compound of claim 1 having (R)-configuration at the phosphorous atom.

Claims 4, 5 and 6 are directed to a composition comprising the compound of claim 1, 2 or 3, respectively, and a pharmaceutically acceptable medium.

III. The auxiliary request held allowable by the opposition division contained only two claims, which were identical to claims 1 and 4 as granted.

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

V. The documents cited during the opposition proceedings included the following:

D1 US 60/909,315 (priority application 1)
D2 US 60/982,309 (priority application 2)
D4 WO 2005/012327
D5 P. Perrone, doctoral thesis, Cardiff University, February 2007
D6 H. Ma *et al.*, The Journal of Biological Chemistry, 2007, 282(41), 29812-20
D7 P. Perrone *et al.*, J. Med. Chem., 2007, 50, 1840-9
D8 M.J. Sofia *et al.*, poster presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow (UK), 9-13 September 2007
D9 E. Murakami *et al.*, Antimicrobial Agents and Chemotherapy, 2008, 52(2), 458-64
D10 J.L. Clark *et al.*, J. Med. Chem., 2005, 48, 5504-8

D12 WO 2005/003147
D18 W.A. Lee *et al.*, Antimicrobial Agents and Chemotherapy, 2005, 49(5), 1898-906
D19 WO 02/08241
D20 C. McGuigan *et al.*, J. Med. Chem., 2006, 49, 7215-26
D22 P. Perrone *et al.*, The Nineteenth International Conference on Antiviral Research, San Juan (Puerto Rico), 7-11 May 2006, abstract No. 100
D33 H. Ma *et al.*, Antiviral Research, 2007, 74(3), abstract No. 23
D34 Email exchange on the publication date of D33 and D35
D35 C. McGuigan *et al.*, Antiviral Research, 2007, 74(3), abstract No. 24
D37 C. McGuigan *et al.*, J. Med. Chem., 2005, 48, 3504-15

VI. In the decision under appeal, the opposition division held that the patent as granted added subject-matter because the application as filed did not disclose the individual diastereomers depicted in claims 2 and 3. Regarding auxiliary request 1, the opposition division concluded that:

- the claimed subject-matter was sufficiently disclosed
- the claimed subject-matter was novel over D4
- the priority right of patent applications D1 and D2 had been validly transferred to the patent proprietor before the filing of the application on which the patent was based
- the claimed subject-matter was disclosed in D2 but not in D1, so auxiliary request 1 enjoyed the priority date of D2 (24 October 2007) but not of D1 (30 March 2007)

- D5 did not belong to the state of the art
- the claimed subject-matter was inventive starting from any of D8, D7 and D6

VII. Each of the patent proprietor and opponents 1, 2, 5, 7, 8, 9 and 10 filed an appeal against the opposition division's decision. Opponents 7, 8 and 9 subsequently withdrew their appeals. Opponents 3, 4 and 6 did not file any appeal.

Consequently, the patent proprietor and opponents 1, 2, 5 and 10 are appellants in these proceedings, while opponents 3, 4, 6, 7, 8 and 9 are parties as of right and respondents to the appellant-patent proprietor's appeal.

VIII. With its statement of grounds of appeal, the appellant-patent proprietor filed 11 sets of claims as auxiliary requests 1 to 11. Auxiliary request 3 was identical to the claim request held allowable by the opposition division.

IX. The board scheduled oral proceedings in line with the parties' requests and gave its preliminary opinion.

X. After two postponements due to the COVID-19 pandemic, oral proceedings were set to be held before the board on 23 and 24 November 2022. Having regard to the occurrence of serious reasons on the part of one of the two patent proprietor's professional representatives in the afternoon of 22 November 2022, the board decided to postpone the start of the oral proceedings to the second of the two scheduled days, i.e. 24 November 2022.

During the oral proceedings, the appellant-patent proprietor renumbered auxiliary requests 1 to 3 filed with the statement of grounds of appeal as auxiliary requests 2, 3 and 1, respectively.

Accordingly, auxiliary request 1 is now identical to the request held allowable by the opposition division. It contains only two claims, which are identical to claims 1 and 4 as granted.

In the evening of 24 November 2022, the board adjourned the oral proceedings until a date after decisions on referrals G 2/21, G 1/22 and G 2/22 have been issued. The board also announced that it would issue an interlocutory decision in writing within four months from 24 November 2022 and that the decision would deal with all matters on which the board had come to a conclusion during the oral proceedings.

XI. The appellant-opponents' and respondent-opponents' cases relevant to this decision can be summarised as follows.

Main request - added subject-matter

Claims 2 and 3 added subject-matter. The criterion for assessing this issue was the gold standard, i.e. whether the claimed compounds were directly and unambiguously disclosed in the application as filed. The appellant-patent proprietor conflated the concept of being directly and unambiguously disclosed with that of being obvious or being able to be carried out.

The application as filed did not disclose any individual compound having a specific configuration at the phosphorous atom. The vague, general statements on

pages 20, 99 and 100 merely made the skilled person aware that the amino acid moiety and the phosphorous atom of the chemical structures subsequently disclosed were chiral and that the chemical structures encompassed the corresponding diastereomers. A conceptual identification of possible diastereomers did not equate to an individualised disclosure of each diastereomer of each compound in the application as filed.

The passage on page 99, line 10 to page 100, line 5 did not refer to compounds or tables but to the subsequent structures, i.e. Formulae II to XXXII. So the passage was not applicable to each of the thousands of compounds listed in Tables II-1 to XXXII-50 and in particular was not applicable to compound IX-25-2. There was also no clear disclosure on page 99, lines 25 to 27 of a generally applicable preference for the (S)-configuration at the chiral carbon atom of the amino acid moiety.

The passage on page 20, lines 8 to 16 generally considered using a racemate or its enantiomers resulting from the chirality at the phosphorous atom. This statement did not disclose the individual diastereomers of each compound defined in the application as filed, including the compound in Example 25.

Example 25 characterised a compound without specifying its configuration at the phosphorous atom and without indicating whether the compound was obtained as a mixture of diastereomers. Example 81 mentioned that "*certain exemplified compounds*" were obtained as mixtures of diastereomers because of the chirality at the phosphorous. It referred then to the separation of

the diastereomers of three examples, which did not include Example 25. So Examples 25 and 81 were not disclosed in combination. Whether it was obvious or possible to separate the diastereomers of Example 25 with the method of Example 81 was irrelevant for assessing added subject-matter.

Claim 2 as filed did not disclose more than Example 25. The use of the term "stereoisomer" in the singular suggested that the claim did not refer to the two diastereomers resulting from the chirality at the phosphorous atom. It could refer to a stereoisomer in relation to the configuration of any of the other six chiral centres of the claimed compounds.

It was established in the case law on the novelty of enantiomers (Case Law of the Boards of Appeal, 9th edn. 2019, I.C.6.2.3) that racemates did not anticipate enantiomers. Decision T 658/91 was outdated and did not comply with the gold standard, established subsequently as the criterion for assessing added subject-matter.

Auxiliary request 1 - priority

The priority application D1 did not disclose the subject-matter of claims 1 and 2 in an enabling manner because the synthesis of the compound was not disclosed. Furthermore, D1 neither contained Example 25 nor the passage on page 20 of the application as filed. It disclosed compound IX-25-2 and a passage equivalent to the one on pages 99 and 100 of the application as filed. However, the combination of these two elements required a triple selection to arrive at the compound of claim 1: Formula IX, (S)-configuration at the amino acid moiety and the set of substituents of compound IX-25-2. So D1 did not disclose the compound of claim

1. The subject-matter of claim 2, interpreted as being directed to the medical use of the compound of claim 1, was not disclosed either.

Auxiliary request 1 - inventive step

The compound of claim 1 was obvious starting from D33, D12, D10, D7 or D4 as the closest prior art.

Starting from D33, the nucleoside RO2433 was the closest prior art. This was the nucleoside on which the compound of claim 1 was based. D33 taught that the triphosphorylated form of RO2433 was highly active against hepatitis C virus (HCV) replication. However, (as submitted by appellant-opponent 10) it was known that RO2433 was inactive (D10, compound 9). Example 82 (entry 25) of the patent application as filed showed that the compound of claim 1 was highly active against HCV replication. Therefore, the compound of claim 1 solved the objective technical problem of providing a form of RO2433 which successfully delivered the biologically active form useful for the treatment of HCV infection (as argued by appellant-opponent 2) or of successfully delivering a biologically active nucleotide (RO-2433-TP) (as argued by appellant-opponent 10).

It was common general knowledge (patent, paragraphs [0014] and [0015]) that nucleosides were poor substrates for kinases and that they may be difficult to phosphorylate, the first phosphorylation step being particularly difficult. D7 solved this problem by derivatising nucleosides as aryl phosphoramidates. The derivatised nucleosides could then be phosphorylated without difficulty up to their triphosphate active form. Moreover, it was generally known (D7, D20, D37,

D18 and D19) that the phenyl phosphoramidate moiety of the compound of claim 1 improved the activity of nucleosides. This was for instance the case of compound 15 in D7, one of the most active compounds in that document. Therefore, a combination of D33 with D7 rendered the compound of claim 1 obvious.

Starting from D12, the nucleoside in the twelfth embodiment (page 39, lines 3 to 9) having a uracil base ($R^4$=OH) constituted the closest prior art; it was the nucleoside on which the compound of claim 1 was based. The embodiment included prodrugs of the nucleoside, which were taught to increase the activity, bioavailability or stability of the nucleoside (page 46, lines 16 to 18). The compound of claim 1 differed from this disclosure by its phenyl phosphoramidate moiety. As there were no comparative data on file against the prodrugs of D12, the objective technical problem was the provision of alternative HCV inhibitors. D7, D37, D18, D20 and D22 proposed the derivatisation of antiviral nucleosides as aryl phosphoramidate prodrugs for improving their activity. In all these documents, nucleosides were derivatised with the phenyl phosphoramidate moiety of the compound of claim 1.

Starting from D10, the closest prior art was compound 9, i.e. the nucleoside on which the compound of claim 1 was based. The authors of D10 found that compound 9 did not inhibit HCV replication. The compound of claim 1 differed from compound 9 in the phenyl phosphoramidate moiety. This difference had the technical effect that the claimed compound inhibited HCV replication. The objective technical problem was therefore how to modify compound 9 of D10 to make it active against HCV.

It was common general knowledge that nucleosides were poor substrates for kinases and that phosphorylation was a limiting step for nucleosides to develop their antiviral effect. The skilled person would have turned to D7, which dealt with this problem. This was even more the case knowing from D33 that the triphosphate of compound 9 of D10 was active against HCV. Following the teaching of D7, the skilled person would have derivatised compound 9 of D10 by adding the aryl phosphoramidate moiety of compound 15 of D7, which was one of the most successful examples.

Starting from D7, the closest prior art was compound 15, which had the aryl phosphoramidate moiety of the compound of claim 1. The latter compound differed from compound 15 in its nucleoside moiety. The data on the inhibition of HCV replication in D7 and the patent could not be directly compared. Therefore, no technical effect could be assigned to the difference with the closest prior art. The objective technical problem was the provision of an alternative compound against HCV.

D7 was aimed at rendering active against HCV nucleosides that had been found to be inactive. D10 taught that compound 9, the nucleoside on which the compound of claim 1 was based, was inactive against HCV. But its triphosphorylated form was known to be active from D33. Therefore, it was obvious to solve the objective technical problem by derivatising compound 9 of D10 with the phenyl phosphoramidate moiety of compound 15 of D7. This was even more true considering that D7 taught (page 1840, right-hand column, third full paragraph) that the approach of phosphoramidate derivatisation had been successful in activating four nucleosides with very different structures.

Starting from D4, the compound of claim 1 resulted from several selections within the generic formula (I) on page 3. The compound of claim 1 was merely an arbitrary choice from a host of possible solutions and, therefore, was obvious.

XII. The appellant-patent proprietor's case relevant to this decision can be summarised as follows.

Main request - added subject-matter

The compounds of claims 2 and 3 were directly and unambiguously disclosed in the application as filed. The basis could be found in:

- compound IX-25-2 in Table IX-25 in light of the explanation on pages 99 and 100 on how the tables were to be understood and the passage on page 20 that defined terms used throughout the application
- Example 25 in light of the passage on page 20
- Example 81, which taught the separation of diastereomers obtained in preceding examples, when applied to Example 25
- claim 2, also in light of the disclosure on page 20

The passage on page 99, line 10 to page 100, line 5 disclosed how to read the structures of the compounds in the tables disclosed subsequently. The preferred compounds were those in which the chiral carbon of the amino acid moiety had (S)-configuration. This was also the configuration of the vast majority of the examples and all the compounds tested in Example 82 having a chiral carbon in the amino acid moiety. So compound IX-25-2 in Table IX-25 had preferably (S)-configuration

at the chiral carbon of the amino acid moiety. Regarding the configuration at the phosphorous atom, the passage on page 99, line 29 to page 100, line 5 explained that the compounds in the tables had (R)- or (S)-configuration, both of which were included. Consequently, compound IX-25-2 had to be read as having (S)-configuration at the chiral carbon of the amino acid moiety and either (R)- or (S)-configuration at the phosphorous atom. This was a clear and unambiguous disclosure of the compounds in claims 2 and 3 as granted.

Example 25 disclosed the compound of claim 1, which was prepared using procedures similar to those described for Examples 5 to 8. So Example 25 was obtained as a mixture of diastereomers due to the chirality at the phosphorous atom.

The passage on page 20, lines 8 to 16 was generally applicable throughout the application. It disclosed the chirality at the phosphorous atom in the compounds of the application and taught that the use of the racemate and/or the resolved enantiomers was contemplated.

The combination of Example 25 and page 20 disclosed a mixture of the diastereomers in claims 2 and 3 as granted and the intention to use the individual diastereomers. So each diastereomer was disclosed.

This was even more the case considering Example 81, which taught that the exemplified compounds obtained as a mixture of diastereomers because of the chirality at phosphorous were separated. The application of the separation method of Example 81 to the mixture of diastereomers of Example 25 inevitably led to each

compound in claims 2 and 3 as granted. This was also a disclosure of the individual diastereomers.

Claim 2 as filed was directed to a compound, its stereoisomer, salt, hydrate, solvate or crystalline form selected from, *inter alia*, compound 25. The chemical name of compound 25 in claim 2 did not specify the configuration at the phosphorous. But page 20, lines 8 to 16 taught that the stereoisomer referred to in the claim was each of the two stereoisomers resulting from the (S)- and (R)-configuration at the phosphorous atom. These were the compounds in claims 2 and 3 as granted.

The case law of the boards, in particular decision T 658/91, supported the appellant-patent proprietor's case. In decision T 658/91, which dealt with a situation closely related to the one at issue, the deciding board established that an explicit reference to the two enantiomers of a given compound was a direct and unambiguous disclosure of each of the two enantiomers. The case law cited by the appellant-opponents did not contradict decision T 658/91.

Auxiliary request 1 - priority

The priority application D1 disclosed the subject-matter of claims 1 and 2 in an enabling manner. The content of D1 was very similar to that of the application as filed. Although D1 did not contain Example 25 and the teaching on page 20 of the application as filed, it disclosed compound IX-25-2 and, on pages 63 and 64, it contained the passage from pages 99 and 100 of the application as filed. The combination of these two elements taught the preference for the (S)-configuration at the chiral carbon atom of

the amino acid moiety. This was also the configuration of the compounds exemplified in D1.

It was apparent from Example 5 of D1 that the skilled person had sufficient information to prepare the compound of claim 1. It was also apparent from its wording that claim 2 was not directed to a medical use but to a composition. The composition of claim 2 had a basis on page 601 of D1.

Auxiliary request 1 - inventive step

The compound of claim 1 was inventive starting from D33, D12, D10, D7 or D4.

Starting from D33, the whole disclosure of the document had to be taken into account. This focused on the metabolism and anti-HCV activity of the cytidine nucleoside R1656. Therefore, the closest prior art was R1656 rather than its uridine analogue RO2433. In any case, D7 did not prompt the skilled person to derivatise RO2433 as an aryl phosphoramidate.

D7 was directed to the activation of antiviral nucleosides known to be inactive as such but highly active in triphosphorylated form. D33 taught that R1656 could be administered without being derivatised and that it was active against HCV via two species, namely the triphosphorylated forms of R1656 and RO2433. The skilled person did not know that RO2433 was inactive and, therefore, had no reason to turn to D7 to provide improved compounds against HCV. The skilled person was even less likely to select the phosphoramidate moiety of a compound which was not the best in D7. Before considering the teaching of D7, the skilled person

needed to test RO2433 or be aware of D10 to realise that RO2433 was inactive.

D12 was not the closest prior art because its data related to a cytidine compound only; no information on the activity of its uridine analogue was disclosed. In any case, the compound of claim 1 had higher anti-HCV activity. The skilled person had no reason to turn to D7 when looking for more active compounds, let alone to compound 15 of D7.

Starting from D10, the closest prior art was the cytidine nucleoside designated as compound 1 rather than its uridine analogue compound 9; D10 focused on compound 1 and referred to compound 9 only to say that it was inactive against HCV. If compound 9 was nevertheless taken as the closest prior art, the compound of claim 1 differed in the aryl phosphoramidate moiety. The claimed compound was highly active against HCV, while compound 9 was inactive. So the objective technical problem was providing a highly active compound for treating HCV infection.

The skilled person was not prompted to turn to D7 and, even if they did, the skilled person could not have reasonable expectations that compound 9 of D10 would become active in the form of an aryl phosphoramidate; the skilled person was not aware of the teaching in D33 that the triphosphate of compound 9 was highly active.

D7 was not the closest prior art. This was even more the case for compound 15, which was not the most active compound in D7. If compound 15 of D7 had to be taken as the closest prior art, the compound of claim 1 differed from it in the nucleoside moiety. This difference resulted in a higher activity against HCV replication;

although the biological results in the patent and D7 could not be directly compared, they suggested that the compound of claim 1 was a better inhibitor of HCV replication. The objective technical problem was the provision of a compound with higher activity against HCV in the replicon assay that did not cause cytotoxicity.

The skilled person had no reason to turn to D10. But even if they did, the skilled person had no reasonable expectations of obtaining a compound more active than compound 15 of D7. The only prompt for derivatising compound 9 of D10 in the way proposed by D7 was the teaching of D33 that compound 9 of D10 was active in triphosphorylated form. But even in this case, the skilled person could not expect that the activated compound would be more active than compound 15 of D7.

Document D4 was not the closest prior art because it was directed to compounds for use in the treatment of cancer rather than HCV infection. Furthermore, there was no suggestion in D4 to select the required substituents within the generic formula on page 3, let alone in combination with uracil as the nucleoside base.

XIII. The parties' final requests were as follows.

The appellant-patent proprietor requested:

- that the decision under appeal be set aside and that the oppositions be rejected, i.e. that the patent be maintained as granted (main request)
- alternatively, that the opponents' appeals be dismissed and that the decision under appeal be upheld, i.e. that the patent be maintained as

amended in the form of auxiliary request 1 as considered allowable by the opposition division (claims resubmitted as auxiliary request 3 with the appellant-patent proprietor's statement of grounds of appeal)

- further alternatively, that the patent be maintained in amended form on the basis of the claims of any of auxiliary requests 2 to 11, filed with the appellant-patent proprietor's statement of grounds of appeal as auxiliary requests 1, 2 and 4 to 11, respectively

The appellant-patent proprietor also requested that the appeal proceedings be stayed at a point where the board's decision would depend on the outcome of any of the pending referral cases G 2/21 or G 1/22 and G 2/22 on the issues of plausibility and entitlement to priority, respectively.

Appellant-opponents 1, 2, 5 and 10 requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Respondent-opponents 7, 8 and 9 withdrew their appeals and neither maintained their earlier requests nor submitted any new requests.

Respondent-opponents 3, 4 and 6 did not file any request in these appeal proceedings.

## Reasons for the Decision

1. The appeals are admissible. They meet the requirements of Articles 106 to 108 and Rule 99(2) EPC.

***Main request (patent as granted)***

*2. Added subject-matter (Article 100(c) EPC)*

This objection was raised by appellant-opponents 1, 2, 5 and 10 and respondent-opponents 7 and 8.

2.1 The objection was primarily raised against claims 2 and 3, which single out the diastereomers of the compound in claim 1 having (S)- or (R)-configuration at the phosphorous atom. Claims 5 and 6 were objected to in so far as they refer to compositions containing one of the compounds of claim 2 or 3.

The basis for claims 2 and 3 in the application as filed given by the appellant-patent proprietor (see also statement of grounds of appeal, point 3.4.1) is the following:

(i) compound IX-25-2 (page 254) in light of the explanation of Tables II-1 to XXXII-50 given on page 99, line 17 to page 100, line 5 and the passage on page 20, lines 8 to 16

(ii) Example 25 (page 683) in light of the passage on page 20, lines 8 to 16

(iii) Example 81 (pages 692 to 693) combined with Example 25

(iv) claim 2 (compound 25, page 702), also in light of the passage on page 20, lines 8 to 16

2.2 The standard of disclosure to be applied for the assessment of added subject-matter is the gold standard, as last confirmed by the Enlarged Board of Appeal in decision G 1/16 (OJ EPO 2018, A70, Reasons 17 to 20). This standard is defined as:

"*what a skilled person would derive directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, from the whole of these documents as filed*".

2.3 Regarding (i), compound IX-25-2 is disclosed in Table IX-25. It has the chemical structure of the compounds of claims 2 and 3 but does not specify the configuration of two chiral centres, namely the phosphorous atom and the chiral carbon atom of the amino acid moiety.

The passage introducing Tables II-1 to XXXII-50 on page 99, lines 25 to 27 reads:

"*it is contemplated that preferred compounds are those...such that the natural L-amino acid (S)-configuration is presented*".

The board agrees with the appellant-patent proprietor that this passage applies to all compounds in the tables, including compound IX-25-2, and that it gives preference to the (S)-configuration at the carbon atom of the amino acid moiety.

As to the configuration of the phosphorous atom, the passage on page 20, lines 8 to 12 discloses that the claimed compounds "*are racemic because of the chirality at phosphorous*", the phosphorous atom being "R" or "S", and that "*the use of the racemate and/or the resolved enantiomers*" is contemplated. Likewise, the sentence bridging pages 99 and 100 generally states that:

- "*Although the structures below do not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible...*"
- "*...phosphorous is either R or S...*"
- "*...the structures below include all possible stereochemical configurations possible for phosphorus*"

The board agrees with the appellant-opponents and respondent-opponents that these general statements on pages 20, 99 and 100 are merely a conceptual description of the diastereomers encompassed by structures II to XXXII owing to the chirality at the phosphorous atom. The reference to the generic structures rather than the specific compounds renders it ambiguous whether the general statements apply to each table and compound disclosed below structures II to XXXII. But more importantly, the general description of the chirality at the phosphorous atom does not constitute a direct and unambiguous individualisation of each of the two diastereomers of each of the thousands of compounds disclosed in Tables II-1 to XXXII-50 having the preferred (S)-configuration at the amino acid moiety.

Therefore, the combination of the cited passages on pages 20, 99 and 100 with Tables II-1 to XXXII-50 does

not individualise the diastereomer of IX-25-2 having (S)-configuration at the chiral carbon of the amino acid moiety and (S)-configuration at the phosphorous atom (compound of claim 2). The same is true for the diastereomer having (S)-carbon and (R)-phosphorous configurations (compound of claim 3).

2.4 Regarding (ii), Example 25 of the application as filed discloses a compound according to claim 1 as granted, i.e. without a specific configuration at the phosphorous atom.

The parties disputed whether the general statements on page 20, lines 8 to 12 could be applied to an example and, in particular, to Example 25. Irrespective of this issue, the general statements on page 20 are conceptual descriptions for the configuration of the phosphorous atom; they do not disclose each diastereomer encompassed by the compounds of the application, let alone by Example 25. Therefore, even if the passage on page 20 could be combined with Example 25, which is left open, this would not lead to a direct and unambiguous disclosure of each compound in claims 2 and 3.

2.5 Regarding (iii), Example 81 states that "*certain exemplified compounds*" were obtained as a mixture of diastereomers because of the chirality at the phosphorous atom. It then explains that the diastereomers were separated in a chiral chromatographic column. Lastly, the example illustrates the separation of the two diastereomers obtained in each of Examples 15, 39 and 49. The diastereomers were characterised by their elution times rather than by their configuration at the phosphorous atom.

The expression "*certain*" in Example 81 suggests that not all the exemplified compounds were obtained as a mixture of diastereomers. The application is silent on which compounds were actually prepared and obtained as a mixture of diastereomers. This is clear only for Examples 15, 39 and 49. Therefore, the board sees no basis in the application as filed for the appellant-patent proprietor's interpretation that the separation method of Example 81 was applied to all the compounds prepared in the application as filed, including Example 25. The fact that the skilled person could separate the diastereomers of Example 25 using the method of Example 81, or that it was obvious to do it, is not a direct and unambiguous disclosure of that separation, let alone of the resulting individual diastereomers.

2.6 Regarding (iv), claim 2 is directed to a compound, its stereoisomer, salt, hydrate, solvate or crystalline form selected from a list including compound 25. It was undisputed that compound 25 is the compound in both Example 25 and claim 1 as granted. The compound has the following chemical name:

(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester.

Like for Example 25, the appellant-patent proprietor combined claim 2 as filed with the passage on page 20, lines 8 to 12. For the reasons explained regarding (ii) (point 2.4), a reading of claim 2 as filed in light of page 20 does not disclose each diastereomer encompassed by compound 25.

The appellant-patent proprietor (statement of grounds of appeal, point 3.9.7) also argued that the normal interpretation of the feature "stereoisomer" in the introductory part of claim 2 as filed had to be as referring to the diastereomers resulting from the undefined configuration at the phosphorous atom. Although that interpretation may make sense, still a general reference to a stereoisomer of the compound of claim 2 is not a direct and unambiguous disclosure of each diastereomer resulting from the undefined configuration at the phosphorous atom of each of the compounds named in claim 2. Furthermore, the board agrees with appellant-opponent 1 that other interpretations of the feature "stereoisomer" in claim 2 also make sense. Compound 25 contains six chiral centres giving rise to a high number of potential diastereomers. Nothing in claim 2 leads to the conclusion that the term "stereoisomer" refers exclusively to the diastereomers resulting from the undefined chirality at the phosphorous atom.

2.7 The parties discussed the case law on the novelty of enantiomers when a racemic mixture is disclosed in the prior art. This case law on disclosure in the context of novelty may indeed be considered for assessing added subject-matter.

The appellant-patent proprietor correctly argued that the circumstances of the case underlying decision T 658/91 were very close to those of the case in hand.

In T 658/91 (Reasons 2.4 and 2.5), the deciding board held that for a compound to be considered individualised in a prior-art document, it was sufficient that the compound be unambiguously identified in that document as being individually

envisaged and that the skilled person could reproduce it. Thus, the mention in the prior-art document that the enantiomers of a racemate were considered an integral part of the invention was not a conceptual piece of information but an unambiguous disclosure of all the enantiomers of the racemates individually disclosed in the examples.

The board in this case does not come to the same conclusion as the deciding board in T 658/91.

The board agrees with appellant-opponent 1 (reply, point 1.2.4), appellant-opponent 5 (reply, paragraph 13) and respondent-opponent 7 (reply, page 3, paragraph 1) that the standard of disclosure to be applied for the assessment of added subject-matter is the gold standard (see point 2.2 above).

The board has explained (points 2.3 to 2.6) why the application as filed does not meet this standard. The generic teaching on pages 20, 99 and 100 drawing attention to the potential presence of diastereomers in the compounds of the invention due to the chirality at the phosphorous atom, or stating that the use of the enantiomers (or diastereomers) or the racemate of the compounds was intended, is not a direct and unambiguous disclosure of each individual diastereomer of each of these compounds.

2.8 Therefore, claims 2 and 3 add subject-matter, and the ground for opposition of Article 100(c) EPC prejudices the maintenance of the patent as granted.

***Auxiliary requests 3, 4, 6, 8, 10***

*3. Added subject-matter (Article 123(2) EPC)*

Each of auxiliary requests 3 (filed as auxiliary request 2), 4, 6, 8 and 10 contains a claim directed to the diastereomer of claim 2 as granted. Therefore, these requests also add subject-matter, contrary to Article 123(2) EPC.

***Auxiliary request 1***

4. Auxiliary request 1 is the amended version of the patent held allowable by the opposition division. Therefore, the principle of prohibition of *reformatio in peius* precludes the consideration by the board of any objection against this request raised exclusively by the parties as of right (respondent-opponents). The fact that claims 1 and 2 of auxiliary request 1 are identical to claims 1 and 4 as granted does not change this situation.

*5. Priority (Article 87 EPC)*

5.1 Same invention - priority application D1

5.1.1 It was common ground that the disclosure of priority application Dl was very similar to that of the application as filed. On pages 63 and 64, D1 discloses the teaching on pages 99 and 100 of the application as filed. Formula IX (page 187) and the embodiment IX-25-2 (page 195) in D1 are also identical to those in the application as filed. In contrast, Dl does not disclose embodiments equivalent to Examples 25 and 81 or the

passage on page 20, lines 8 to 12 of the application as filed.

Compound IX-25-2 is identical to the compound in claim 1 of auxiliary request 1 apart from not specifying the configuration at the chiral carbon atom of the amino acid moiety and the phosphorous atom. However, as set out for added subject-matter (point 2.3), the board agrees with the appellant-patent proprietor that the penultimate full sentence on page 63 of D1 expressing an explicit preference for the compounds having (S)-configuration at the chiral carbon of the amino acid moiety is applicable to all the compounds in Tables II-1 to XXXII-50. This includes compound IX-25-2 in Table IX-25. This preference is confirmed by the fact that all the compounds illustrated and tested in D1 (Table on pages 621 and 622) have (S)-configuration at the chiral carbon of the amino acid moiety.

Therefore, D1 directly and unambiguously discloses the compound in claim 1 of auxiliary request 1.

5.1.2 Appellant-opponent 1 argued (statement of grounds of appeal, point 3.2.2) that the compound of claim 1 was not disclosed because D1 did not contain sufficient information for the skilled person to prepare it without undue burden.

This argument fails. As noted by the appellant-patent proprietor at the oral proceedings before the board, Example 5 of D1 (pages 614 and 615) discloses the synthesis of a compound which differs from the compound of claim 1 only in that it is a methyl ester instead of an isopropyl ester. The skilled person could exchange

methyl with isopropyl in the method of Example 5 and prepare the compound of claim 1 without undue burden.

5.1.3 Regarding the priority of claim 2 (claim 4 as granted), appellant-opponent 1 (statement of grounds of appeal, point 3.2.3.1) argued that the claim was a first medical use claim because it was directed to a pharmaceutical composition. It went on to conclude that D1 did not plausibly disclose any medical use for the compound of claim 1. Therefore, D1 did not disclose the composition of claim 2 in an enabling manner.

This objection fails, too. Claim 2 reads:

"*A composition comprising the compound of claim 1 and a pharmaceutically acceptable medium*".

The board sees no room in the wording of this claim for adopting appellant-opponent 1's interpretation that claim 2 is directed to a medical use. It was not contested that the composition of claim 2 has a basis on page 601 of D1 and that the skilled person is able to prepare it without undue burden.

5.1.4 Therefore, the board concludes that D1 discloses the same invention in an enabling manner as claimed in auxiliary request 1.

5.2 Same invention - priority application D2

None of the appellant-opponents contested that priority application D2 discloses the subject-matter of auxiliary request 1. Appellant-opponent 1 acknowledged this during the oral proceedings notwithstanding its written submissions concerning claim 2 (appellant-opponent 1's statement of grounds of appeal, page 15,

point 3.2.3.2). Indeed, the compound in Example 25 of D2 is the compound in claim 1 of auxiliary request 1. The compound is also disclosed as compound 25 in claim 1 of D2.

Therefore, the board concludes that D2 discloses the same invention in an enabling manner as claimed in auxiliary request 1.

5.3 Entitlement to priority

It was a matter of dispute between the parties whether the applicant, when filing the application on which the patent is based, was entitled to claim priority from the earlier applications D1 and D2 and, in this context, whether the applicant was the successor in title of the applicants that filed priority applications D1 and D2.

In the referral cases pending before the Enlarged Board of Appeal G 1/22 and G 2/22, the questions posed by the referring board are the following:

"*I. Does the EPC confer jurisdiction on the EPO to determine whether a party validly claims to be a successor in title as referred to in Article 87(1)(b) EPC?*

*II. If question I is answered in the affirmative*

*Can a party B validly rely on the priority right claimed in a PCT-application for the purpose of claiming priority rights under Article 87(1) EPC*

*in the case where*

*1) a PCT-application designates party A as applicant for the US only and party B as applicant for other designated States, including regional European patent protection and*

*2) the PCT-application claims priority from an earlier patent application that designates party A as the applicant and*

*3) the priority claimed in the PCT-application is in compliance with Article 4 of the Paris Convention?"*

The outcome of referral cases G 1/22 and G 2/22 is therefore relevant for the board's decision on the validity of the priorities claimed in the case in hand. For this reason, in line with the appellant-patent proprietor's request and in the absence of any objection against a possible stay of the proceedings, the board decided not to take a decision on the issue of entitlement to priority but to await the outcome of these referral cases. Accordingly, if need be, this issue will be dealt with once decisions on G 1/22 and G 2/22 have been handed down.

6. *Novelty (Article 54 EPC)*

None of the appellant-opponents contested the novelty of the subject-matter of auxiliary request 1.

7. *Inventive step (Article 56 EPC)*

The appellant-opponents cited documents D33, D35, D12, D10, D9, D8, D7, D6 and D4 as starting points for the assessment of inventive step. Some of these documents were also used as combination documents for arguing

obviousness. In this decision, the board deals exclusively with the inventive-step objections involving only documents published before the earliest priority date, i.e. 30 March 2007. These are the objections starting from D33, D12, D10, D7 and D4 and using as combination documents D33, D10, D7, D37, D35, D22, D20, D19 and/or D18.

It was undisputed that D7 and D33 were published before 30 March 2007. D7 states at the footer of its first page that it was published online on 17 March 2007. The email exchange gathered in D34 demonstrates that D33 and D35 were available online on 22 February 2007.

For the following assessment of inventive step, the board did not need to take post-published evidence into consideration. Therefore, the outcome of the currently pending referral case G 2/21 on the issue of plausibility was not relevant for the outcome of the decision on this point and, to that extent, there was no need for the board to consider staying the appeal proceedings in view of referral G 2/21.

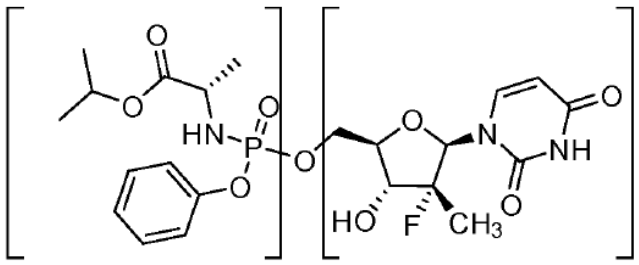
7.1 Background

The patent (paragraph [0001]) is concerned with the preparation of nucleoside prodrugs that inhibit HCV replication and their use for treating HCV infection.

According to the patent (paragraphs [0014] to [0015]), the antiviral active form of nucleosides is generally the triphosphate. However, nucleoside triphosphates are not stable in biological systems. For a nucleoside to exert its antiviral activity, it must first be delivered to the infected cell and then be triphosphorylated by cell kinases. It appears that some

nucleosides are poor substrates for cell kinases, the first phosphorylation step being usually the most difficult one. To improve the delivery of antiviral nucleosides to infected hepatic cells and to circumvent the limitations of the monophosphorylation step, the patent proposes formulating the nucleosides as a phosphoramidate prodrug.

The compound of claim 1 is the phenyl phosphoramidate prodrug of a nucleoside. It can be conceptually divided into two parts: a uridine nucleoside responsible for the HCV activity and a phosphoramidate prodrug moiety which overcomes the delivery and phosphorylation issues of the nucleoside.



phosphoramidate nucleoside

7.2 Starting from D33 as the closest prior art

In the written appeal proceedings, this objection was raised by appellant-opponent 2 (statement of grounds of appeal, section VI.3.3) and appellant-opponent 10 (reply, paragraphs 29 to 41). At the oral proceedings before the board, appellant-opponent 1 also raised an inventive-step objection starting from D33, but its arguments were essentially those already put forward by appellant-opponent 10.

Appellant-opponent 10 referred (reply, paragraphs 30 and 32) to abstract 23 in D35 (Ma) as a starting point

for the assessment of inventive step, but this is the same abstract as in D33. The arguments of appellants-opponents 2 and 10 are therefore considered with reference to D33 only.

7.2.1 D33 summarises a study on the metabolism and the inhibition of HCV replication in human hepatocytes of the cytidine-based nucleoside R1656 (β-D-2'-fluoro-2'-C-methyl-cytidine). After incubation of hepatocytes with R1656, the authors of D33 found that R1656 was the major intracellular compound but that the deaminated analogue RO2433 (β-D-2'-fluoro-2'-C-methyl-uridine) and the 5'-phosphorylated derivatives of both R1656 and RO2433 were also present. The triphosphorylated forms of R1656 and RO2433 increased with time to become the major phosphorylated species at steady state. Both triphosphorylated species inhibited HCV replication with comparable potencies, the triphosphorylated RO2433 having a longer half-life. Based on these observations, the authors of D33 suggested the investigation of once daily regimens of R1656 for the treatment of HCV infection.

7.2.2 RO2433 is the nucleoside on which the compound of claim 1 is based. Appellant-opponents 1, 2 and 10 considered that this compound was the closest prior art.

The appellant-patent proprietor argued that this starting point was not the closest prior art and that its choice involved hindsight. However, in accordance with the established case law of the boards, a conclusion that the subject-matter claimed is inventive can only be reached after assessing this requirement starting from all the possible pieces of closest prior art. Therefore, the appellant cannot argue against assessing inventive step starting from RO2433.

7.2.3 The compound of claim 1 differs from RO2433 by its phosphoramidate moiety.

According to document D10, cited in paragraph [0018] of the patent in suit, RO2433 is not active against HCV (D10, page 5506, compound 9 in Figure 3 and Table 2, and right-hand column, last sentence of the first paragraph). In contrast, the patent shows in Example 82 (Table, Example 25) that the compound of claim 1 inhibits in-cell HCV replication at sub-micromolar concentrations ($EC_{90}$= 0.39 µM).

7.2.4 Based on this technical effect, the objective technical problem is the provision of an effective compound for the treatment of HCV infection.

Appellant-opponent 2 (statement of grounds of appeal, page 25, penultimate paragraph) defined the problem as the provision of a form of compound RO2433 useful for the treatment of HCV. Similarly, appellant-opponent 10 (reply to the appeal, point 35) formulated the problem as how to successfully deliver the biologically active form of RO2433. These formulations of the problem are biased by the knowledge that the inactivity of RO2433 against HCV replication is overcome by administering it in the form of a prodrug. With this bias, the appellant-opponents introduced an impermissible pointer into the solution in their formulation of the objective technical problem.

7.2.5 Appellant-opponents 2 and 10 combined D33 with D7.

D7 (abstract) deals with the activation of nucleosides that do not inhibit HCV replication in a cell-based test but which are known to be good HCV replication

inhibitors in triphosphorylated form. D7 (page 1840, right-hand column, paragraph 3) explains that the cause for the inactivity of the parent nucleoside may be its poor membrane permeation and/or the fact that it is a poor substrate for phosphorylation by cell enzymes.

Appellant-opponent 10 (reply, paragraphs 31 and 34) relied on two elements for justifying the combination of D33 with D7: on the one hand, the alleged common general knowledge disclosed in paragraphs [0014] and [0015] of the patent that some nucleoside analogues are poor substrates for the cellular kinases responsible for phosphorylation; on the other hand, the disclosure in D10 that RO2433 was inactive against HCV. Appellant-opponent 2 (statement of grounds of appeal, page 27, third paragraph) argued that there was a generic teaching in the art that the activity of antiviral nucleosides could be enhanced by their derivatisation with the phenyl phosphoramidate moiety of the compound of claim 1.

These arguments are not convincing.

The patent does not acknowledge that the information in its paragraphs [0014] and [0015] is common general knowledge. Furthermore, it cannot be derived from the teaching in paragraphs [0014] and [0015] that RO2433 would be inactive, let alone that this would be because it is a poor substrate for kinases.

As to D10, it does not qualify as a document representing common general knowledge; it is a report on the results of particular scientific research. So the information in D10 (compound 9 in Figure 3 and Table 2) that RO2433 was not active against HCV did not

belong to the skilled person's common general knowledge.

It follows that the information that RO2433 does not inhibit HCV replication in cell cannot be used to construe the skilled person's mindset when reading D33.

Starting from compound RO2433 in D33 and faced with the problem of finding an effective compound for treating HCV infection, the skilled person had no motivation to turn to D7 because they did not know that RO2433 was inactive against HCV. The skilled person was even less likely to know that the reasons for the lack of activity of RO2433 were those intended to be overcome by the authors of D7, namely poor membrane permeation and/or a poor phosphorylation rate by cell enzymes. Therefore, the combination of D33 with D7 is based on hindsight.

As correctly noted by the appellant-patent proprietor at the oral proceedings before the board, the skilled person would have first needed to combine D33 with D10. Only then could the skilled person have been motivated to turn to D7. Therefore, this necessary two-step combination of documents is based on hindsight and indicates that the compound of claim 1 was not obvious starting from D33.

7.2.6 Appellant-opponent 2 (statement of grounds of appeal, page 27, third paragraph and page 16, last paragraph to page 18, first paragraph) also noted that the phenyl phosphoramidate moiety of the compound of claim 1 had been previously used for improving the activity of different nucleosides not only in D7 but also in D20 (Tables 1 and 2), D37 (Table 4), D18 (page 1899 and Tables 1 and 5) and D19 (page 41, Table 4). However,

for the same reason that there was no motivation for the skilled person to combine D33 with D7, there was also no motivation for combining D33 with D20, D37, D18 or D19. Like D7, these documents suggest the derivatisation of inactive or poorly active antiviral nucleosides as aryl phosphoramidate prodrugs to render them active. But the poor antiviral activity of RO2433 was known neither from D33 nor from any of D7, D20, D37, D18 and D19.

7.2.7 Appellant-opponent 10 (reply, paragraph 38 to 40) referred to the combination D33 with abstract 24 in D35, noting that this abstract was a summary of D7. Therefore, the combination of D33 with abstract 24 in D35 also rests on hindsight.

7.3 Starting from D12 as the closest prior art

This objection was raised by appellant-opponent 5 (statement of grounds of appeal, paragraphs 33 to 42 and 51, 52 and 84).

7.3.1 D12 (page 1, lines 6 to 8) is directed to the use of nucleoside analogues for treating *Flaviviridae* infections, especially HCV. The twelfth embodiment of D12 (page 39) is a generic formula comprising two nucleosides: a cytidine analogue ($R^4$=$NH_2$) and a uridine analogue ($R^4$=OH). The uridine analogue is the nucleoside on which the compound of claim 1 is based. The embodiment also encompasses pharmaceutical acceptable salts or prodrugs of the nucleosides. Appellant-opponent 5 (statement of grounds of appeal, paragraphs 34 to 36 and paragraph 51) considered that an appropriate prodrug of the uridine analogue was the closest prior art.

7.3.2 The appellant-patent proprietor argued that the uridine analogue prodrug of D12 was not the closest prior art. As noted for D33 (point 7.2.2), the appellant-patent proprietor cannot argue against assessing inventive step starting from that nucleoside.

7.3.3 The compound of claim 1 differs from the uridine analogue prodrug in the twelfth embodiment of D12 in its phenyl phosphoramidate moiety.

Appellant-opponent 5 (statement of grounds of appeal, paragraph 52) was right in that there are no comparative data on file against the (unspecified) uridine analogue prodrugs of D12. However, the patent shows in Example 82 that the compound of claim 1 is active against HCV replication at sub-micromolar concentrations.

7.3.4 Therefore, the objective technical problem is the provision of an effective compound for the treatment of HCV infection.

7.3.5 Appellant-opponent 5 combined D12 with D7, D37, D18, D20 and D22.

The appellant-patent proprietor correctly noted at the oral proceedings before the board that D12 contains biological examples (Tables 1 to 9 on pages 90 to 94) only for the cytidine analogue. D12 is silent on any activity of the uridine analogue or its phosphorylated forms against HCV replication.

D10 and D33 do not represent common general knowledge, and D12 does not refer to them. Consequently, the skilled person neither knew that the uridine analogue of D12 was inactive against HCV (D10) nor that it was

active in triphosphorylated form (D33). Therefore, for the reasons explained for D33 (point 7.2.5), the skilled person, faced with the problem of providing an effective compound for the treatment of HCV infection, had no motivation to apply the teaching of D7 to the uridine analogue of D12, let alone to prepare the phosphorylated prodrug of claim 1 as granted. Neither would the skilled person have turned to D37 (page 3507, Table 4), D18 (compound GS7340 in Tables 1 and 5), D20 (compound 4c in Table 1) or D22 (abstract 100, paragraph 2). Like D7, all these documents relate to the derivatisation of inactive or poorly active antiviral nucleosides as aryl phosphoramidate prodrugs to render them active. Therefore, the compound of claim 1 was not obvious starting from D12.

7.4 Starting from D10 as the closest prior art

This objection was raised by appellant-opponent 1 (statement of grounds of appeal, section 4.4.1.2).

7.4.1 D10 is concerned with the design and synthesis of new inhibitors of HCV replication. Among other compounds, D10 tested the nucleoside on which the compound of claim 1 is based, designated as compound 9, and found it to be inactive (page 5506, Table 2 and right-hand column, first paragraph, last sentence). Appellant-opponent 1 considered that compound 9 was the closest prior art.

The appellant-patent proprietor contended that compound 9 of D10 could not be the closest prior art. As explained for the objection starting from D33 (point 7.2.2), the appellant-patent proprietor cannot argue against assessing inventive step starting from compound 9 of D10.

7.4.2 The compound of claim 1 differs from compound 9 of D10 by its phenyl phosphoramidate moiety. As when starting from D33 (point 7.2.3), this difference has the technical effect that the claimed compound is highly active against HCV replication, while compound 9 is inactive.

7.4.3 The objective technical problem is providing an effective compound for the treatment of HCV infection.

Appellant-opponent 1 (statement of grounds of appeal, page 23, fourth paragraph) defined the objective technical problem as how to modify compound 9 of D10 to make it active against HCV. This formulation of the problem is biased by the knowledge that the triphosphate of compound 9 of D10 is active against HCV. With this bias, appellant-opponent 1 introduced an impermissible pointer into the solution in the objective technical problem.

7.4.4 Appellant-opponent 1 combined D10 with D7.

Faced with the problem of providing an effective compound for the treatment of HCV infection, the skilled person had no reason to turn to D7 because they did not know why compound 9 of D10 was inactive. The skilled person was not aware that the inactivity of compound 9 was linked to its poor cell permeation and/or its difficulties for being phosphorylated by cell kinases and, therefore, could not have any reasonable expectation that compound 9 would become active in the form of an aryl phosphoramidate suggested by D7. To combine D10 with D7, the skilled person would have first needed to benefit from the knowledge in D33 that the triphosphate of compound 9 was active against HCV.

Therefore, the combination of D10 with D7 rests on hindsight. As for the situation starting from D33, this necessary two-step combination of documents is based on hindsight and indicates that the compound of claim 1 was not obvious starting from D10.

7.5 Starting from D7 as the closest prior art

This objection was raised by appellant-opponent 1 (statement of grounds of appeal, page 18, lines 1 and 2 and page 23, last line).

7.5.1 Like the patent, D7 is concerned with finding new antiviral agents against HCV. As explained above (point 7.2.5), the nucleosides activated in D7 do not inhibit HCV replication but are known to be active in triphosphorylated form. The inactivity of the unmodified nucleosides is believed to be caused by a poor membrane permeation and/or a poor ability to be phosphorylated by cell kinases. The solution proposed in D7 was derivatising the inactive nucleoside as an aryl phosphoramidate.

7.5.2 Appellant-opponent 1 considered compound 15 of D7 the closest prior art.

7.5.3 The compound of claim 1 has the same phosphoramidate moiety as compound 15 of D7; it differs in the nucleoside moiety.

Appellant-opponent 1 (statement of grounds of appeal, page 18, third paragraph from the bottom) correctly noted that the compound of claim 1 and compound 15 of D7 have been shown to be active against HCV replication at submicromolar concentrations (patent, Example 82, and D7, Table 1) but that their activity cannot be

directly compared. Therefore, if post-published evidence is not taken into consideration, no technical effect can be associated with this difference.

7.5.4 The objective technical problem may then be formulated as the provision of an alternative compound against HCV.

7.5.5 In the written proceedings, appellant-opponent 1 combined D7 with D6 and D8. This objection is not dealt with in this decision because D6 and D8 were published after the earliest priority date. Whether D6 and D8 form part of the state of the art within the meaning of Article 54(2) EPC depends on the question of the validity of the priority claimed from priority application D1 (see Article 89 EPC), in relation to which the board decided to stay proceedings and await the decisions in referral cases G 1/22 and G 2/22.

At the oral proceedings before the board, appellant-opponent 1 combined D7 with D10. It has been explained above (point 7.4.1) that D10 deals with the search for new inhibitors of HCV replication and that compound 9 was inactive. Compound 9 is the nucleoside on which the compound of claim 1 is based.

D7 proposes the derivatisation of nucleosides that are inactive against HCV but that become highly active when triphosphorylated. Although D10 shows that compound 9 is not active against HCV, it fails to disclose that compound 9 is highly active in triphosphorylated form. Therefore, compound 9 of D10 was not a candidate for the method of D7, and the skilled person had no motivation to derivatise it according to D7.

To be motivated to derivatise compound 9 of D10 with the method of D7, the skilled person would have needed the additional information in D33 that the triphosphorylated form of compound 9 of D10 (called RO2433-TP in D33) was highly active against HCV. Again, this necessary two-step combination of documents based on hindsight indicates that the compound of claim 1 was not obvious starting from D7.

7.6 Starting from D4 as the closest prior art

Appellant-opponent 1 (statement of grounds of appeal, point 4.4.1.1) raised an inventive-step objection based on D4 as the closest prior art but did not develop any problem-solution approach. At the oral proceedings before the board, appellant-opponent 1 did not wish to make further submissions on this objection.

7.6.1 D4 (abstract and page 1, lines 3 and 4) relates to the derivatisation of nucleosides as phosphoramidates for use in the treatment of cancer.

The appellant-patent proprietor argued that D4 could not be the closest prior art because it did not relate to the treatment of HCV infection. The appellant-patent proprietor cannot argue against assessing inventive step starting from D4 (point 7.2.2). Nevertheless, the board concludes that the claimed subject-matter is also inventive when starting from D4.

7.6.2 Appellant-opponent 1 referred to the generic formula (I) on page 3 of D4 and conceded that multiple selections were needed to arrive at the compound of claim 1. Indeed, at least nine substituents need to be selected, namely R, R', R", Q, X, Y, Ar, Z, and Z'.

7.6.3 The technical effect brought about by this multiple selection is that the compound of claim 1 inhibits HCV replication, while the compounds of D4 are taught to be anti-cancer agents.

7.6.4 Based on this technical effect, the objective technical problem could also be formulated as providing an effective compound for the treatment of HCV infection.

7.6.5 It is apparent that D4 contains no pointer suggesting that the compound of claim 1 would be suitable for the treatment of HCV infection. Appellant-opponent 1 did not combine D4 with any additional document. Therefore, the compound of claim 1 is inventive starting from D4.

7.7 For the above reasons, the board concludes that the compound of claim 1 is inventive over the cited prior art available to the public before the earliest priority date.

This conclusion applies equally to claim 2, which is directed to a composition comprising the compound of claim 1.

8. *Staying appeal proceedings*

The board has dealt with all objections involving items of prior art published before the earliest priority date and has reached a stage of the appeal proceedings at which the consideration of further objections depends on the outcome of the currently pending referral cases G 1/22 and G 2/22 on entitlement to priority, for which reason the board decided to await the decision by the Enlarged Board of Appeal on this issue (see also point 5.3 above).

Thus, the inventive-step objections involving documents D6, D8 and D9 remain to be discussed at forthcoming oral proceedings to be scheduled once the decisions in these referral cases have been handed down.

The issue of whether post-published evidence may be taken into account may become relevant for assessing the inventive-step objections involving D6, D8 and D9. Therefore, the outcome of the presently pending referral case G 2/21 on plausibility may also be relevant.

At the oral proceedings before the board, the appellant-patent proprietor requested that appeal proceedings be stayed at an appropriate point in view of the pending referrals G 2/21, G 1/22 and G 2/22. No party objected against a possible stay of proceedings.

In light of the above considerations, the board decided to stay the appeal proceedings until a date when decisions on the pending referral cases G 2/21, G 1/22 and G 2/22 have been issued by the Enlarged Board of Appeal.

*9. Interlocutory decision*

The case has come to a point at which a stay of proceedings is considered required. At the date of the oral proceedings, no information existed on when a decision would be handed down in the three pending referral cases G 2/21, G 1/22 and G 2/22. This, together with the fact that one of the five board members will retire on 1 March 2023, led the board to decide, as announced at the oral proceedings, to issue an interlocutory decision on the issues for which the

parties could provide their comments at the oral proceedings and for which the board closed the debate.

This interlocutory decision avoids a situation, detrimental to procedural economy and legal certainty, in which the board in a new composition may need to re-hear the parties on matters dealt with at the oral proceedings of 24 November 2022 (Article 8(1) RPBA 2020). By this interlocutory decision each new member will be bound to the same extent as the other members (Article 8(2) RPBA 2020).

**Order**

**For these reasons it is decided that:**

- The ground for opposition of Article 100(c) EPC prejudices the maintenance of the patent as granted.
- Each of auxiliary requests 3 (filed as auxiliary request 2 with the appellant-patent proprietor's statement of grounds of appeal), 4, 6, 8 and 10 add subject-matter, contrary to Article 123(2) EPC.
- D1 and D2 disclose the same invention in an enabling manner as claimed in auxiliary request 1.
- The subject-matter of auxiliary request 1 is inventive starting from any of documents D4, D7, D10, D12 and D33, excluding any combination with documents published after the earliest priority date of the patent.
- The appeal proceedings are stayed until the decisions in referral cases G 2/21, G 1/22 and G 2/22 have been issued.

The Registrar: The Chairman:

B. Atienza Vivancos P. de Heij

Decision electronically authenticated