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Datasheet for the decision of 8 March 2021

Case Number: T 2200/17 - 3.3.02

Application Number: 01961695.2

Publication Number: 1301519

IPC: C07F9/6561, C07H19/20, G01N33/53, A61K31/675, A61P31/12, A61P35/00

Language of the proceedings: EN

Title of invention:
PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES AND METHODS FOR SELECTING AND MAKING SAME

Patent Proprietor:
GILEAD SCIENCES, INC.

Opponents:
Teva Pharmaceutical Industries Ltd
Swindell & Pearson Limited
STRAWMAN LIMITED
HEXAL PHARMA AG

Headword:
TENOFOVIR PRODRUG / GILEAD SCIENCES

Relevant legal provisions:
EPC Art. 54, 56, 87
RPBA Art. 12(1), 12(2)
RPBA 2020 Art. 13(2)

Keyword:
Priority - validity of priority date (yes)
Novelty - (yes)
Inventive step - (yes)
Unsubstantiated objection - admitted (no)
Submissions after summons - admitted (no)

Decisions cited:
T 0181/82, T 0197/86, T 1193/06, T 1488/08, T 0576/11, T 1391/13, T 1232/14, T 1287/14

Catchword:

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Case Number: T 2200/17 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 8 March 2021

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 August 2017 concerning maintenance of the European Patent No. 1301519 in amended form.

Composition of the Board:

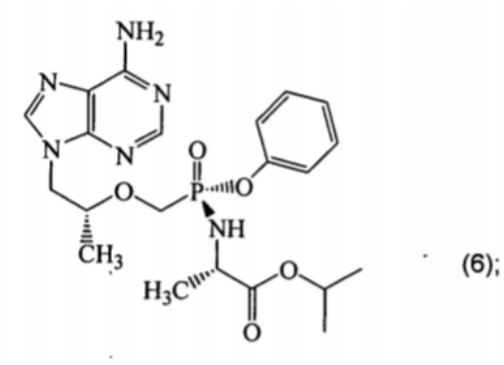
Chairman M. O. Müller
Members: M. Maremonti
L. Bühler

Summary of Facts and Submissions

I. The appeals by opponents 1, 2 and 4 (hereinafter "appellant 1, appellant 2 and appellant 4") lie from the interlocutory decision of the opposition division, according to which European patent No. 1 301 519 (hereinafter "the patent") in its form modified on the basis of the then pending main request and the invention to which it relates meets the requirements of the EPC.

II. The main request held allowable by the opposition division contains five claims, independent claim 1 of which reads as follows:

"*1. A compound of structure (6)*



(6);

or its salts and solvates."

Claim 2 defines a particular embodiment of the compound of claim 1; claim 3 is directed to a composition comprising the compound of claim 1; and claims 4 and 5 are directed to compounds 1 and 3, respectively, for use in treating an HIV infection.

III. The following documents were cited, *inter alia*, during the opposition proceedings:

D3: WO 95/07920 A

D4: WO 96/29336 A

D5: Robbins B.L. *et al.*, "*Anti-Human Immunodeficiency Virus Activity and Cellular Metabolism of a Potential Prodrug of the Acyclic Nucleoside Phosphonate 9-R-(2-Phosphonomethoxypropyl) adenine (PMPA), Bis(isopropyloxymethylcarbonyl) PMPA*", Antimicrobial Agents and Chemotherapy, Mar. 1998, pages 612 to 617

D11: McGuigan C. *et al.*, "*Novel nucleoside phosphoramidates as inhibitors of HIV: Studies on the stereochemical requirements of the phosphoramidate amino acid*", Antiviral Chemistry & Chemotherapy, 7(4), 1996, pages 184 to 188

D22: WO 99/05150 A

D25: Eisenberg E.J. *et al.*, "*Metabolism of GS-7340, a novel phenylmonophosphoramidate intracellular prodrug of PMPA, in blood*", Nucleosides, Nucleotides & Nucleic Acids, 20(4-7), 2001, pages 1091 to 1098

D26: Chapman H. *et al.*, "*Practical synthesis, separation, and stereochemical assignment of the PMPA pro-drug GS-7340*", Nucleosides, Nucleotides & Nucleic Acids, 20(4-7), 2001, pages 621 to 628

D27: Chapman H. *et al.*, "*urification of PMPA amidate prodrugs by SMB chromatography and X-ray crystallography of the diastereomerically pure GS-7340*", Nucleosides Nucleotides & Nucleic Acids, 20(4-7), 2001, pages 1085 to 1090

D29: McGuigan C. *et al.*, "*Synthesis and anti-HIV activity of some novel chain-extended phosphoramidate derivatives of d4T (stavudine): esterase hydrolysis as a rapid predictive test*

for antiviral potency", Antiviral Chemistry & Chemotherapy, 9, 1998, pages 109 to 115

D34: Jones R.J. and Bischofsberger N., "*Minireview: nucleotide prodrugs*", Antiviral Research, 27, 1995, pages 1 to 17

D35: McGuigan C. *et al.*, "*Intracellular Delivery of Bioactive AZT Nucleotides by Aryl Phosphate Derivatives of AZT*", Journal of Medical Chemistry, 36, 1993, pages 1048 to 1052

D36: Balzarini, J. *et al.*, "*Mechanism of anti-HIV action of masked alaninyl d4T-MP derivatives*", Proc. Natl. Acad. Sci. USA, 93, 1996, pages 7295 to 7299

D37: McGuigan C. *et al.*, "*Aryl Phosphoramidate Derivatives of d4T Have Improved Anti-HIV Efficacy in Tissue Culture and May Act by the Generation of a Novel Intracellular Metabolite*", Journal of Medical Chemistry, 39, 1996, pages 1748 to 1753

D38: Siddiqui A.Q. *et al.*, "*Design and Synthesis of Lipophilic Phosphoramidate d4T-MP Prodrugs Expressing High Potency Against HIV in Cell Culture: Structural Determinants for in Vitro Activity and QSAR*", Journal of Medical Chemistry, 42, 1999, pages 4122 to 4128.

D39: Saboulard D. *et al.*, "*Characterization of the Activation Pathway of Phosphoramidate Triester Prodrugs of Stavudine and Zidovudine*", MOLECULAR PHARMACOLOGY, 56, 1999, pages 693 to 704

D42: Shaw J.P. *et al.*, "*Metabolism and Pharmacokinetics of Novel Oral Prodrugs of 9-[(R)-2(phosphonomethoxy)propyl]adenine (PMPA) in*

Dogs", Pharmaceutical Research, 14(12), 1997, pages 1824 to 1829

D43: Arimilli M.N. *et al.*, "*Synthesis, in vitro biological evaluation and oral bioavailability of 9-[(R)-2(phosphonomethoxy)propyl]adenine (PMPA) prodrugs*", Antiviral Chemistry & Chemotherapy, 8(6), 1997, pages 557 to 564

D45: McGuigan C. *et al.*, "*Synthesis, anti-human immunodeficiency virus activity and esterase lability of some novel carboxylic ester-modified phosphoramidate derivatives of stavudine (d4T)*", Antiviral Chemistry & Chemotherapy, 9, 1998, pages 473 to 479

D49: Lynch T. *et al.*, "*LC/MS determination of the intracellular concentration of two novel aryl phosphoramidate prodrugs of PMPA and their metabolites in dog PBMC*", Nucleosides, Nucleotides & Nucleic Acids, 20(4-7), 2001, pages 1415 to 1419

D60: Birkus G. *et al.*, "*Activation of 9-[(R)-2-[[(S)-[[(S)-1-(Isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]-methoxy]propyl]adenine (GS-7340) and Other Tenofovir Phosphonoamidate Prodrugs by Human Proteases*", MOLECULAR PHARMACOLOGY, 74(1), 2008, pages 92 to 100

D63a: Letter of the applicants of D3 during the examination proceedings of D3 dated 19 March 1999

D67: Krise J.P. and Stella V.J., "*Prodrugs of phosphates, phosphonates, and phosphinates*", Advanced Drug Delivery Reviews, 19, 1996, pages 287 to 310

D68: Farquhar D. *et al.*, "*5'-[4-(Pivaloyloxy)-1,3,2-dioxaphosphorinan-2-yl]-2'-deoxy-5-fluorouridine: A Membrane-Permeating Prodrug of 5-Fluoro-2'-deoxyuridylic Acid (FdUMP)*", Journal of Medical Chemistry, 38, 1995, pages 488 to 495

IV. The opposition division came to, *inter alia*, the following conclusions.

- The main request fulfilled the requirements of Articles 83 and 123(2) EPC.
- The priority was validly claimed.
- The subject-matter of the main request was novel over document D3.
- The subject-matter of the main request involved an inventive step starting from either the compound tenofovir disoproxil (TD)/tenofovir disoproxil fumarate (TDF), D3 or D4 as the closest prior art.

V. In their statements of grounds of appeal, the appellants raised objections under Article 123(2) EPC and Rule 80 EPC. They also objected to the validity of the priority, novelty and inventive step of the claimed subject-matter.

Appellant 1 filed the following new document:

A070: Ballatore C. *et al.*, "*Synthesis and Evaluation of Novel Amidate Prodrugs of PMEA and PMPA*"

VI. In its reply to the statements of grounds of appeal, the patentee (hereinafter "respondent") rebutted the arguments of the appellants and maintained that the main request fulfilled all requirements of the EPC.

VII. Opponent 3 withdrew its opposition by letter dated 6 October 2017. Thus, it is not party to these appeal proceedings.

VIII. The parties were summoned to oral proceedings in accordance with their requests.

IX. In preparation for the oral proceedings, the board issued a communication pursuant to Article 15(1) RPBA 2020 in which it expressed, *inter alia*, the preliminary opinion that the claimed subject-matter was entitled to the claimed priority, was novel and involved an inventive step.

X. By letter dated 22 January 2021, the respondent requested that the oral proceedings be held by videoconference.

XI. By letter dated 25 January 2021, appellant 4 informed that it would not attend the oral proceedings.

XII. By a subsequent communication, the board informed the parties that oral proceedings would be held by videoconference.

XIII. By letter dated 4 February 2021, appellant 1 made additional submissions.

XIV. By letter dated 8 February 2021, appellant 2 informed that it would not attend the oral proceedings.

XV. Oral proceedings before the board were held on 8 March 2021 by videoconference in the absence of appellant 2 and appellant 4, pursuant to Rule 115(2) EPC and Article 15(3) RPBA 2020.

XVI. Final requests

The appellants requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeals be dismissed, or, alternatively, that the patent be maintained on the basis of the claims of the auxiliary request filed on 5 August 2016.

The respondent further requested that appellant 2's objection of added matter under Article 123(2) EPC not be admitted into the appeal proceedings and that appellant 1's submissions in paragraphs A.17 to A.28 of its letter dated 4 February 2021 (XIII above) not be admitted into the appeal proceedings.

XVII. The objections of the appellants, in so far as relevant to the present decision, are summarised as follows.

- The subject-matter of claim 1 did not comply with Article 123(2) EPC and Rule 80 EPC.

- The subject-matter of claim 1 was not entitled to the priority date.

- Since the priority was not valid, intermediate documents D25 to D27 and D49 represented prior art to be considered for novelty under Article 54(2) EPC. All these documents disclosed the claimed compound (6) and thus were novelty-destroying for the subject-matter of claim 1.

- Even assuming that the priority was valid, document D3 anticipated the claimed subject-matter.

- As regards inventive step, the compound TD/TDF as disclosed in D22, D42 and D43 or, alternatively, D3 (in combination with D63a) or D4 could be regarded as the closest prior art.

- No technical effect of the claimed compound over each of these starting documents had been shown in the patent.

- In this respect, appellant 1's submissions in paragraphs A.17 to A.28 of its letter dated 4 February 2021 pointing to several contradictions

and discrepancies contained in examples 9 to 11 of the patent had to be taken into account.

- The application as filed did not make it plausible that an enrichment of Tenofovir (TFV) in lymphoid tissues had been achieved by using the claimed compound over the disclosure of D4.

- The claimed compound merely resulted from arbitrary selections within the closest prior art compounds, without involving any inventive step.

- Even considering the technical problem as the provision of an improved prodrug over the known compound TD/TDF, the skilled person would have found the claimed compound suggested by all documents D11, D29, D34, D35, D39 and D45, also taking into account the teaching of D67 and D68.

- Therefore, the subject-matter of claim 1 did not involve an inventive step.

XVIII. The respondent essentially counter-argued as follows.

- The objection under Article 123(2) EPC had not been substantiated in the grounds of appeal. Thus, it should not be admitted into the proceedings pursuant to the Rules of Procedure of the Boards of Appeal.

- No objection under Rule 80 EPC could be raised since the amendment referred to by the appellants had been made in the examination and not the opposition proceedings.

- The subject-matter of claim 1 was entitled to priority since no selections had to be made within

the priority application to arrive at the claimed compound.

- D25 to D27 and D49 were intermediate documents. Thus, they could not be used against novelty.

- Starting from the general disclosure of D3, at least four undisclosed selections had to be made to arrive at the claimed compound. Therefore, D3 was not novelty-destroying.

- The inventive-step submissions of appellant 1 in paragraphs A.17 to A.28 of its letter dated 4 February 2021 were entirely new and should not be admitted into the proceedings pursuant to Article 13(2) RPBA 2020.

- Documents D3 and D4 were not suitable as the closest prior art. The only suitable starting point was the known prodrug TD/TDF.

- The objective technical problem had to be seen as the provision of an improved orally bioavailable prodrug of TFV for the treatment of HIV having enhanced potency and enrichment of TFV in lymphoid tissues compared to plasma.

- None of the prior art invoked by the appellants suggested the claimed compound as a solution to this technical problem.

- It had to be concluded that the subject-matter of claim 1 involved an inventive step.

- Even if D3 or D4 was assumed to be the closest prior art, the claimed compound was still inventive.

- These two documents represented highly speculative disclosures describing vast classes of largely theoretical compounds of unknown anti-HIV activity and oral bioavailability.

- Neither D3 nor D4 provided any guidance that would have led the skilled person to the claimed compound.

- It had to be concluded that the main request was allowable.

Reasons for the Decision

Admittance of the appellant 2's objection under Article 123(2) EPC into the proceedings

1. Appellant 2 (statement of grounds of appeal, page 3) objected to the subject-matter of claim 1 of the main request under Article 123(2) EPC.

   The respondent requested that this objection not be admitted into the proceedings.

1.1 The board observes that under Article 12(1) RPBA 2007, the appeal proceedings shall be based on, *inter alia*, the statement of grounds of appeal. Under Article 12(2) RPBA 2007, the statement of grounds of appeal shall contain the party's **complete case**, expressly specifying, *inter alia*, all the facts, arguments and evidence relied on.

1.2 In its statement of grounds of appeal (page 3, second paragraph), appellant 2 did not substantiate its objection under Article 123(2) EPC with any argument but merely referred to its notice of opposition.

1.3 The board holds that the mere reference to the notice of opposition amounts to an unsubstantiated objection that does not constitute a case for appellant 2 under Article 123(2) EPC within the meaning of Article 12(2) RPBA 2007.

1.4 In its communication issued in preparation for the oral proceedings (point 5.2), the board had already expressed its concerns as regards the admittance of the objection under Article 123(2) EPC raised by appellant 2. No reply from appellant 2 contesting this preliminary findings was filed.

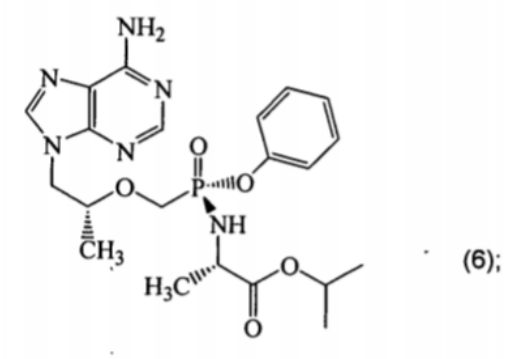
1.5 Since no case had been filed under Article 123(2) EPC by appellant 2 in the appeal proceedings, the board decided that its objection under Article 123(2) EPC was not part of the appeal proceedings (see also T 1232/14, reasons, points 3.1 to 3.8; T 1193/06, reasons, point 2; T 1391/13, reasons, point 4; T 1488/08, reasons, point 2.1; and T 0576/11, reasons, point 3.1).

Main request - claim 1 - compliance with Rule 80 EPC

2. Appellant 2 argued that the amendment to claim 23 as filed and contained in claim 1 of the main request had not been occasioned by a ground for opposition, thus contravening Rule 80 EPC.

2.1 Claim 1 of the main request reads as follows, with the amendment to independent claim 23 as filed highlighted by the board:

"*1. A compound of structure (6)*



(6);

~~*and*~~ ***or*** *its salts and solvates.*"

2.2 However, this amendment was carried out during the examination proceedings. In fact, claim 1 of the main request is identical to claim 1 as granted. Therefore, contrary to the appellant 2's view, its subject-matter is not objectionable under Rule 80 EPC.

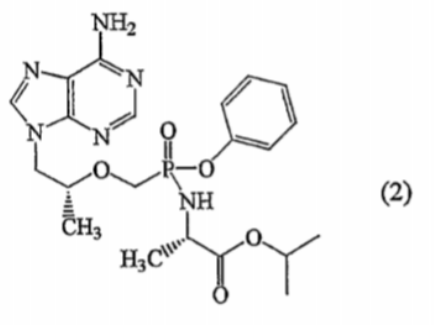
Main request - claim 1 - validity of the priority

3. Appellants 2 and 4 objected to the validity of the priority of the patent. They argued that the priority application only disclosed the compound of structure (6) as such. Its salts and solvates, also mentioned in claim 1 of the main request, were not directly and unambiguously disclosed in the priority application. They only resulted from multiple selections from different lists within the priority application without any proper basis.

3.1 The board disagrees.

Page 3 of the priority application discloses the following:

"*A preferred compound of this invention has the structure (2)*



(2)

and its enriched diasteromers, salts, free base and solvates."

The compound of structure (2) only differs from the compound of claim 1 in that the stereochemistry at the phosphorous atom is not indicated. However, diastereomers, salts and solvates of compound (2) are explicitly disclosed. This passage of the priority application, by not defining the stereochemistry, implicitly discloses salts and solvates of each diastereomer of compound (2). In fact, the diastereomer of compound (2) corresponding to the claimed compound (6) is explicitly individualised on page 6 of the priority application.

3.2 Therefore, the board comes to the conclusion that the subject-matter of claim 1 of the main request is directly and unambiguously disclosed in the priority application. No selection is necessary to arrive at the claimed subject-matter. Consequently, the priority of the patent is validly claimed (Article 87 EPC).

Main request - claim 1 - novelty under Article 54 EPC

4. Appellants 2 and 4 cited intermediate documents D25 to D27 and D49 against the novelty of the claimed subject-matter in case the priority of the patent was found to be invalid.

However, in view of the above conclusion of the board on the validity of the priority, intermediate documents

D25 to D27 and D49 do not represent prior art to be considered in the assessment of novelty under Article 54 EPC.

5. Appellant 4 additionally argued that the claimed compound lacked novelty over the disclosure of document D3, particularly over structure 38.2.3.1 disclosed in table 1 on page 36 of D3.

5.1 However, the board notes that structure 38.2.3.1 is merely one of an extremely vast number of exemplary compounds disclosed in tables 1 to 4 on pages 25 to 64 of D3. Moreover, even though it encompasses the claimed compound (6), it represents a generic disclosure in view of the presence of the substituent R_4. The latter can be selected from 13 possibilities as listed on page 27, lines 1 to 5, only one of which is isopropyl, i.e. as required by claim 1. Moreover, the stereochemistry at the three chiral sites indicated in claim 1 (II above) is not indicated for compound 38.2.3.1 of D3.

5.2 Therefore, to arrive at the claimed compound (6), the skilled person would have had to select first the generic structure 38.2.3.1 out of a myriad of exemplary compounds, then isopropyl as the substituent R_4 and finally the stereochemistry at the three chiral sites corresponding to that of compound (6) of claim 1. No preference or any other pointer for the above selections is disclosed in D3.

5.3 In view of the above, the board comes to the conclusion that the claimed compound is not directly and unambiguously disclosed in D3. The subject-matter of claim 1 and claims 2 to 5 referring back to claim 1 is thus novel over D3 (Article 54 EPC).

Admittance of the appellant 1's submissions on inventive step as contained in paragraphs A.17 to A.28 of its letter dated 4 February 2021 into the proceedings

6. In its letter dated 4 February 2021, i.e. shortly before the oral proceedings, appellant 1 included submissions pointing to several contradictions and discrepancies allegedly present in examples 9 to 11 of the patent (paragraphs A.17 to A.28). Appellant 1 thus sought to raise doubts about whether these examples reliably demonstrated a technical effect of the claimed compound over known prodrugs.

The respondent requested that these submissions not be admitted into the proceedings under Article 13(2) RPBA 2020.

6.1 Appellant 1's submissions on inventive step as contained in paragraphs A.17 to A.28 of its letter dated 4 February 2021 had not been made in its statement of grounds of appeal nor before the summons to oral proceedings. This was not disputed by appellant 1. Thus, these submissions represent an amendment to appellant 1's case made after notification of the summons to oral proceedings. Under Article 13(2) RPBA 2020, any amendment to a party's appeal case made at this stage of the proceedings shall, in principle, not be taken into account unless there are **exceptional circumstances**, which have been **justified with cogent reasons** by the party concerned (emphasis added by the board).

6.2 Appellant 1 did not put forward any exceptional circumstances or cogent reasons justifying the filing of the above-mentioned submissions only with its letter dated 4 February 2021. It merely stated during the oral proceedings that it intended to rely on them for its case on inventive step.

6.3 The board does not see any exceptional circumstance or cogent reason that could have justified the filing of the above-mentioned submissions only with the letter dated 4 February 2021 either. Therefore, in exercising its discretion under Article 13(2) RPBA 2020, the board decided not to admit appellant 1's submissions on inventive step contained in paragraphs A.17 to A.28 of its letter dated 4 February 2021 into the proceedings.

Main request - claim 1 - inventive step under Article 56 EPC

7. The closest prior art

The compounds Tenofovir disoproxil (TD) and Tenofovir disoproxil fumarate (TDF) as disclosed in, for instance, documents D22, D42 and D43 were indicated by the opposition division, appellants 2 and 4, and the respondent to be the closest prior art. Appellant 1 indicated instead documents D3 and D4 as possible starting points for the assessment of inventive step.

8. Starting from TD/TDF

8.1 The board notes that TD and TDF (D22: pages 13 and 14; D42: table 1 on page 1825; D43: figure 2 on page 561), represent, in the same way as the claimed compound (6), prodrugs of the parent drug (R)-9-[2-(phosphonomethoxy) propyl]adenine (known as (R)-PMPA or Tenofovir, "TFV" in the following), i.e. molecules able to release TFV in infected tissues, especially for the treatment of HIV. Moreover, TD and TDF (D22, page 1, lines 9 to 13; D42, abstract; D43, page 557) were especially developed to improve the oral bioavailability, an aim shared by the patent (paragraph [0025] and examples 10 and 11). The board thus considers TD and TDF as disclosed in these documents to be a suitable starting point for the assessment of inventive step.

8.2 It is undisputed that the claimed compound (6) differs from TD/TDF in that the central P atom is bound to one phenyloxy group and one L-alanilyl amidate isopropoxy ester group in place of the two [(isopropoxycarbonyl)oxy]methyl (POC) groups of TD/TDF.

The technical problem

8.3 The respondent (reply to the appeals, page 10, point 5.28 and 5.29) referred to paragraphs [0007] to [0009], [0025], [0029], [0111] and [0112] and examples 9 to 11 of the patent that demonstrated an improved anti-HIV potency and an enrichment of the parent drug TFV in the lymphoid tissues as compared to plasma of the claimed compound (hereinafter "parent drug enrichment") over TD/TDF. It formulated the technical problem accordingly.

8.4 Appellant 4 (statement of grounds of appeal, page 12) recognised an improvement achieved by the claimed compound (6) over TD/TDF and formulated the technical problem as the provision of an improved orally bioavailable TFV prodrug.

Appellant 2 (statement of grounds of appeal, page 8) instead pointed out that example 9 only concerned a comparison between the claimed compound (6) as such and TDF, while neither the fumarate salt of the claimed compound (6) nor TD had been tested. Moreover, TDF had not been tested in example 10. Thus, no technical effect had been shown over the entire claimed scope. The technical problem had to be merely seen in the provision of an alternative prodrug.

8.5 The board notes that example 9 of the patent (page 20) compares the anti-HIV activity and the plasma stability of the claimed compound (GS 7340) versus TDF. Table 1

reports a 10-fold activity increase and a 200-fold stability increase for the claimed compound over TDF.

Paragraph [0111] of the patent reports by reference to example 10 a 21-fold enrichment in lymphoid tissues of the parent drug TFV after administration of the claimed compound compared to administration of TD.

Enrichment in lymphoid tissues after administration of the claimed compound (GS 7340) compared to administration of TDF is further confirmed in example 11 (table 7, page 30).

Thus, examples 9 to 11 show an enhanced potency and parent drug enrichment achieved by the claimed compound (6), compared to both TD and TDF.

8.6 Examples 9 to 11 of the patent are carried out in solution. Thus, the board concurs with the opposition division (appealed decision, point 19.3.4.1) that the initial form of the prodrug, i.e. whether used as a free base or a salt, is not significant for the result. Appellant 2 has not contested this finding of the opposition division in its statement of grounds of appeal.

8.7 Therefore, starting from TD/TDF, the objective technical problem lies in the provision of an orally bioavailable prodrug of TFV for the treatment of HIV having enhanced potency and parent drug enrichment.

Obviousness of the claimed solution

8.8 Appellants 2 and 4 referred to various documents that in their opinion would have prompted the skilled person to modify TD/TDF to arrive at the claimed compound (6). In particular, they invoked documents D67 and D68.

8.9 The board notes that D67 (abstract) concerns prodrugs of phosphate, phosphonates and phosphinates. According

to D67 (page 289), the prodrugs should display adequate stability for formulation and adequate solubility in the gastrointestinal tract to allow dissolution. Moreover, they should also have good permeability and revert to the parent drug after permeation (schemes 1 and 2 on page 289). Various prodrugs are reviewed in D67, especially prodrugs of zidovudine (AZT) and 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA), the latter being structurally similar to TFV. A bis(pivaloyloxymethyl) prodrug of TFV known from the prior art is mentioned in passing on page 296, left-hand column. However, no technical effect of such a prodrug compared to TD/TDF is mentioned. Also, the problem of enrichment of parent drugs in lymphoid tissues is not reported in D67.

D68 (abstract, conclusion) concerns the prodrug FdUMP of the antitumor drug 5-fluorouracil (FU). Activity against HIV is not mentioned, let alone prodrugs of TFV.

8.10 Therefore, neither D67 nor D68 contain any indication that would have prompted the skilled person to modify TD/TDF by replacing the two POC groups of TD/TDF by the phenyloxy group and L-alanilyl amidate isopropoxy ester group of the claimed compound (6) when aiming to solve the posed technical problem.

8.11 Appellants 2 and 4 also referred to documents D11, D29, D34, D35, D39 and D45. However, D11, D29, D35, D39 and D45 concern phospho**r**amidate prodrugs of the parent drugs stavudine (d4T) and AZT. Even if substituents similar to those of the claimed compound (6) are disclosed (D11: figure 1; D29: figure 1; D35: scheme I; D39: page 696; D45: figure 1), no indication is provided that such substituents might also be used for TFV, let alone for solving the posed technical problem over TD/TDF. The same is especially true for the

passage of D35 on page 1050, left-hand column, invoked by appellant 4. Here, D35 suggests that the synthetic approach described for the parent drug AZT should also be applied to other antiviral nucleotide analogues, e.g. PMEA. However, no concrete prodrugs of PMEA are mentioned, let alone prodrugs of TFV.

D34 is a general review of nucleotide prodrugs. Prodrugs of, *inter alia,* PMEA are disclosed (page 4) albeit having different substituents compared to the claimed compound (6). Prodrugs of TFV are not mentioned, let alone any technical effect over TD/TDF.

8.12 As a consequence, these additional documents invoked by appellants 2 and 4 would also not have prompted the skilled person to modify TD/TDF by replacing the two POC groups of TD/TDF with the phenyloxy group and L-alanilyl amidate isopropoxy ester group of the claimed compound (6) with the aim of solving the posed technical problem.

8.13 For the reasons set out above, the board comes to the conclusion that the subject-matter of claim 1 involves an inventive step when starting from TD/TDF as the closest prior art.

9. Starting from document D4

9.1 Appellant 1 argued that document D4 should be regarded as the closest prior art. This was contested by the respondent, who, however, commented on inventive step also starting from D4 (XVIII above).

9.2 The board notes that D4 (pages 1, 2 and 4), like the patent, concerns masked analogues showing antiviral activity against, *inter alia,* HIV. The disclosed compounds are said to be highly active against HIV in both thymidine kinase and thymidine kinase rich cells.

As regards the parent drugs, D4 refers to AZT, d4T and PMEA (page 2, lines 17 to 35, page 13, lines 4 to 10).

9.3 Even though TFV is not mentioned as a parent drug, it is not entirely unreasonable to consider D4 as a suitable starting point for the assessment of inventive step. It will thus be assumed in appellant 1's favour that D4 is a suitable closest prior art.

9.4 Appellant 1 pointed to formula (8) on page 13 of D4, which encompasses the claimed compound (6). The claimed subject-matter differs from formula (8) of D4 in the specific selection of the substituents B, T^1, T^2, Ar, R^1 and J, to be respectively adenine, hydrogen, methyl, phenyl, a side-chain of L-alanine and isopropyl, and in the specified stereochemistry at the P atom. These distinguishing features were not disputed by the respondent.

The technical problem starting from D4

9.5 According to the respondent, the technical problem had to be seen in the provision of an orally bioavailable prodrug for the treatment of HIV having enhanced potency and parent drug enrichment over the known prodrugs TD/TDF. This was also the problem that could be derived from the opposed patent (see e.g. paragraph [0007]).

9.5.1 As set out above (point 8.5), examples 9 to 11 of the patent show that compound (6) as defined in claim 1, i.e. a compound in which the substituents B, T^1, T^2, Ar, R^1 and J in formula (8) of D4 are chosen as required by claim 1, leads to an improvement of HIV activity and an enhanced parent drug enrichment relative to TD and TDF.

The problem referred to by the respondent is thus credibly solved and therefore forms the objective technical problem.

9.5.2 In contrast to this conclusion, appellant 1 argued that the comparison with TD and TDF was the "wrong comparison" since these compounds did not reflect the teaching of the closest prior art document D4. This comparison could thus not prove any enhanced potency and parent drug enrichment over D4.

9.5.3 The board agrees with this argument, but it is beside the point. The above objective technical problem does not refer to an enhanced potency and parent drug enrichment **relative to D4**, a problem which would indeed not be credibly solved and would thus indeed not constitute the objective technical problem. Instead, it refers to an enhanced potency and parent drug enrichment **relative to TD and TDF**. The board agrees that to demonstrate an inventive step on the basis of an unexpected effect (improvement or advantage), comparative tests have to meet certain criteria. These normally include the proper choice of the structurally closest comparative compound to be taken from the closest state of the art (T 181/82, OJ EPO 1984, page 401, reasons, point 5; T 197/86, OJ 1989, page 371, reasons, point 4). This requirement is based on the concept of the structural dependence of properties of chemical substances, i.e. on the principle that properties are essentially determined by the structures of substances. Given that two substances are expected to have similar properties in view of their (close) structural similarity, an unexpected effect (improvement or advantage) has to be normally demonstrated by comparing the claimed compound with the structurally closest compound in the state of the art in a comparable use. However, in the case at issue, the

suggested comparison with one or more compounds encompassed by formula (8) of D4 instead of TD and TDF is not justified since formula (8) is a generic disclosure that offers no specific reference for comparison. Not a single compound falling under formula (8) of D4 was actually prepared in D4, let alone tested for any antiviral activity. For this reason, the merely notional compounds falling under formula (8) of D4 cannot qualify for use in a technically meaningful comparison. Also, appellant 1's criticism that the use of TD/TDF as a reference compound in the patent did not constitute a proper comparison is not justified. This comparison is not arbitrary since it truly reflects the impact of the structural changes in the claimed compound (6) compared to TD and TDF, which represented the prodrugs of TFV known before the priority date of the patent. It was not argued that TD and TDF were tendentiously chosen as reference compounds to support an improvement. Thus, the comparison provided by the patent is fair and can be taken into consideration when assessing inventive step.

9.5.4 Appellant 1 further argued that the examples of the patent showed that the selections made within formula (8) of D4 to arrive at the claimed compound (6) did not result in any technical effect and were thus arbitrary. In particular (statement of grounds of appeal, pages 5 and 6, points 23 to 27), the results reported in tables 4 and 6 and figure 3 of the patent demonstrated that the claimed selections of alanine for R1 and isopropyl for J within formula (8) of D4 did not show any improvement over other tested compounds like GS 7114 (having an ethyl group instead of isopropyl) and GS 7342 (having aminobutyric acid instead of alanine) also encompassed by formula (8) of D4. Moreover, the results presented in table 5 were contradictory to those reported in table 6. Table 5

showed that GS 7114, a compound not falling under claim 1 but under formula (8) of D4, performed better than the claimed compound in terms of plasma stability and conversion to TFV in MT-2 cells. Table 6 instead reported a better performance of the claimed compound over GS 7114. Consequently, the claimed compound (6) was "an arbitrary or obvious individualised compound" from the compounds covered by formula (8) of D4 (point 33 of appellant 1's statement of ground of appeal). Thus, the technical problem over D4 had to be merely seen as the individualisation of a particular anti-HIV compound within those compounds of D4.

9.5.5 The board acknowledges that the results reported in the patent referred to by appellant 1 indeed show that the two compounds GS 7114 and GS 7342 falling under formula (8) of D4 are as good as or even better than the claimed compound in terms of potency and parent drug enrichment. The board also acknowledges that this implies that these two specific compounds have an enhanced potency and parent drug enrichment compared to TD and TDF. The board finally acknowledges that if one were to start from these two specific compounds tested in the patent and covered by formula (8) of D4, the objective technical problem would indeed be merely to arbitrarily select (or individualise) a specific compound out of those covered by formula (8) of D4.

9.5.6 However, the appellant's line of argument puts the cart before the horse as it implies that an improvement or advantage must be demonstrated in comparison to the compounds GS 7114 and GS 7342 instead of TD/TDF and that the objective technical problem was a mere selection. This approach is flawed. Selecting the specific compounds of formula (8) of D4 that have been shown in the patent to have enhanced potency and parent drug enrichment over TD and TDF and arguing that

compared to these specific compounds the claimed compound was an arbitrary selection (or an "individualisation") uses knowledge available only in the patent and not disclosed at all in D4. More specifically, these compounds tested in the patent, though in theory falling under formula (8) of D4, are not individualised in D4. Therefore, these compounds are not representative of the disclosure of D4. In fact, as was pointed out above, not a single compound falling under formula (8) of D4 was actually prepared in D4, let alone tested for any anti-HIV activity in general or any enhancement of HIV potency and parent drug enrichment in particular compared to TD and TDF. The general reference in D4 to activity against HIV and the disclosure of, *inter alia*, the generic formula (8) is not a disclosure of GS 7114 and GS 7342 but at best an invitation to identify compounds covered by formula (8) of D4 having anti-HIV activity. Hence, in view of this generic nature of the disclosure in D4, appellant 1's formulation of the objective technical problem as being a mere individualisation of a particular anti-HIV compound within the compounds covered by formula (8) of D4 must fail.

9.5.7 Therefore, the board's conclusion made above, namely that the objective technical problem lies in the provision of an orally bioavailable prodrug for the treatment of HIV having enhanced potency and parent drug enrichment over the known prodrugs TD/TDF, remains valid.

9.6 In the context of whether or not the respondent was allowed to rely on post-published evidence (here document D60), appellant 1 contested during the oral proceedings that the application as filed had made it plausible that the claimed compound led to an enhanced parent drug enrichment over D4. However, what matters

here is an enhanced parent drug enrichment over TD and TDF rather than D4. Furthermore, the application as filed contains the same examples 9 to 11 as present in the patent. The conclusion above that the patent shows and thus makes it plausible that the claimed compound leads to enhanced potency and parent drug enrichment over TD and TDF thus applies to the application as filed as well. Hence, appellant 1's argument must fail.

Obviousness of the claimed solution when starting from D4

9.7 Appellant 1 based its arguments regarding the obviousness of the claimed compound on the allegation that the claimed selections of the substituents B, T^1, T^2, Ar, R^1 and J within the general formula (8) of D4 were not purposeful, i.e. did not lead to any effect and were purely arbitrary.

9.8 However, for the reasons set out above, this argument is not convincing.

9.9 Even if the claimed selections of the substituents B, T^1, T^2, Ar, R^1 and J within the general formula (8) of D4 are singularly mentioned in D4, D4 contains no indication that would have prompted the skilled person to select all of them in combination, let alone when seeking a solution to the posed technical problem.

9.10 In fact, even if D4 (page 13, lines 4 to 10) refers to the compounds of formula (8) as also PMEA analogues, PMEA being similar to TFV (the parent drug in the opposed patent), none of the compounds actually prepared in D4 (pages 21 to 46) concerns PMEA prodrugs, let alone TFV prodrugs, having the substituents of the claimed compound (6). Even less does D4 disclose or suggest that the compounds of formula (8) lead to any potency or parent drug enrichment enhanced over the known prodrugs TD and TDF. In fact, no parent drug

enrichment or comparison with TD or TDF is found in D4. Rather, masked compounds of d4T are disclosed and tested in D4 for activity against HIV (pages 48 to 60).

9.11 Therefore, the skilled person would not have been prompted by D4 to make the selections necessary to arrive at the claimed compound (6) when aiming to solve the posed technical problem.

9.12 Appellant 1 also invoked documents D35 to D39 and D45, which it said, in combination with D4, would have led the skilled person to the claimed compound.

9.13 These arguments are also not convincing. As regards D35, D39 and D45, these documents concern phospho**r**amidate prodrugs of the parent drugs d4T and AZT. Even if substituents similar to those of the claimed compound are disclosed (D35: scheme I; D39: page 696; D45: figure 1), no indication is provided that such substituents might also be used for TFV, let alone to solve the posed technical problem. This is especially true for the passage of D35 on page 1050, left-hand column, invoked by appellant 1. As set out above, D35 suggests here that the synthetic approach described for the parent drug AZT should also be applied to other antiviral nucleotide analogues, e.g. PMEA. However, no concrete prodrugs of PMEA are mentioned, let alone prodrugs of TFV.

Also, D36 to D38 (D36: abstract, figure 1, D37: abstract, figure 1; D38: abstract, scheme 1) concern phospho**r**amidate prodrugs of the parent drug d4T. Even if substituents similar to those of the claimed compound are disclosed, no indication is provided that such substituents might also be used for TFV, let alone to solve the posed technical problem.

9.14 Therefore, these additional documents would also not have prompted the skilled person to make the selections within formula (8) of D4 necessary to arrive at the claimed compound (6) when aiming to solve the posed technical problem.

9.15 As a consequence, the board comes to the conclusion that the claimed subject-matter involves an inventive step when starting from D4 as the closest prior art.

10. Starting from document D3

10.1 Appellant 1 argued that document D3 should also be regarded as a possible closest prior art. In particular, the starting point had to be seen in structure 38.2.3.1 (table 1, page 36), which had the most features in common with the claimed compound (6). Document D63a confirmed that structure 38.2.3.1 of D3 was especially relevant since a new claim 15 had been included which was directed to this structure. Its use as an antiviral agent had been specified in claim 29. In this respect, appellant 1 referred to decision T 1287/14, confirming that an example and not the document as a whole had to be regarded as the closest prior art.

The respondent contested that D3, let alone structure 38.2.3.1, could represent a suitable starting point. Nevertheless, it commented on inventive step also starting from D3 (XVIII above).

10.2 The board notes that D3 (page 1, lines 7 to 11) concerns nucleotide analogues said to exhibit antitumor activity. However, D3 (pages 65 and 66) additionally states that the hydrolysis products described also have activity against several viruses, *inter alia,* HIV. PMEA is reported among other compounds to have antimicrobial activity and also to be active against HIV (page 65, lines 21 to 22, page 66, lines 17 to 34). As hydrolysis

products, TFV is also mentioned among others (page 75, line 34, to page 76, line 8).

10.3 In view of this general disclosure, the board considers that D3 may also represent a suitable starting point for the assessment of inventive step. However, contrary to appellant 1's view, D3 as a whole and not the specific structure 38.2.3.1 should be regarded as the closest prior art.

10.4 In fact, 38.2.3.1 is only one among a myriad of structures falling under the general structure (L1)(L2)P(O)-Z-B disclosed on page 25, line 11, of D3. The groups L1, L2, Z and B are listed in table 1 on pages 25 and 26 of D3. Compounds of this general structure are listed starting on page 28, line 3, to page 51, line 20, by reference to the numbers assigned to L1, L2, Z and B in table 1 according to the convention "L1.L2.Z.B". Further compounds of the general structure are listed by reference to the numbers assigned to L1, Z and B in tables 2 and 3 on pages 51 to 53 and 54 to 56, respectively, and by reference to the numbers assigned to L1, L2 and B in table 4 on pages 58 to 60. These compounds merely represent exemplary candidates to be subsequently screened until the desired substrate specificity is found (page 64, line 20, to page 65, line 2). Although combination 38.2.3.1 (found on page 36, line 10, as part of a list of permutations of the substituents of table 1 in the formula (L1)(L2)P(O)-Z-B) encompasses the claimed compound (see the novelty discussion above), no compound of this formula was prepared in D3, let alone tested for anti-HIV activity. When a PMEA analogue was prepared in D3, it was merely tested for its activity against herpes viruses and not HIV (example 2, page 107, example 4, page 109).

Therefore, the skilled person would not have recognised structure 38.2.3.1 as a suitable prodrug of TFV for acting against HIV since no disclosure at all of this nature is present in D3. The skilled person would not have regarded this structure as a promising springboard towards the claimed invention.

10.5 Also, D63a does not change this finding. In fact, D63a is a submission of the applicants of D3 during examination proceedings that includes a new set of claims, comprising, *inter alia,* a new claim 15 directed to structure 38.2.3.1. However, no explanation for this addition is mentioned in D63a, let alone any identification of 38.2.3.1 as being a TFV prodrug to be used against HIV.

10.6 As regards T 1287/14 invoked by appellant 1, the document regarded there as the closest prior art (D5) was directed to a process for coating a ceramic honeycomb monolith to be used as a catalyst. The general teaching of the document was exemplified in a single example 1 disclosing a specific coating composition. The entrusted board regarded this example 1 as the starting point for assessing inventive step (reasons, point 5.2.1).

However, the case at issue is totally different from the one dealt with in T 1287/14 since 38.2.3.1 is not a set of features disclosed in combination as an individualised example or embodiment but merely one of an extremely vast number of potential candidate compounds merely disclosed as permutations of combinations of substituents to the general formula (L1)(L2)P(O)-Z-B that have to be subsequently screened and selected for their activities. Therefore, the present decision does not contradict T 1287/14.

The technical problem starting from D3

10.7 Appellant 1 argued that starting from structure 38.2.3.1 of D3, the technical problem had to be merely seen as the individualisation of a particular anti-HIV compound of structure 38.2.3.1.

10.8 However, for the reasons set out above, the skilled person would not have started from structure 38.2.3.1 but rather from the disclosure of D3 as a whole. Thus, the claimed subject-matter differs from this disclosure in the specific structure of compound (6) as defined in claim 1.

10.9 For the same reasons as expressed above as regards D4, the objective technical problem thus lies in the provision of an orally bioavailable prodrug for the treatment of HIV having enhanced potency and parent drug enrichment over the known prodrugs TD/TDF.

Obviousness of the claimed solution when starting from D3

10.10 Appellant 1 argued that the skilled person would have known before the priority date of the patent that TFV was active against HIV. It referred to D5 and D48 in this respect. On the basis of this knowledge, they would have recognised that all structures disclosed in D3 of the type *.*.3.1, given the definition of the numbers 3 and 1 on pages 25 and 26 of D3, included the molecule of TFV and thus represented potential TFV prodrugs. It would have been matter of routine experimentation to arrive specifically at the claimed compound.

10.11 The board disagrees for the following reasons.

10.11.1 To arrive at the claimed compound, the skilled person would have had to select first the generic structure 38.2.3.1 out of a huge number of permutations mentioned

in D3, then isopropyl as the substituent R_4 within this structure and finally the stereochemistry at the three chiral sites corresponding to that of compound (6) of claim 1.

10.11.2 No preference for the above selections is indicated in D3, and no indication is provided in D3 that would have prompted the skilled person to consider the generic structure 38.2.3.1. In fact, as stated above, no compounds falling under this structure were actually prepared in D3, let alone tested for any activity. Moreover TFV is only mentioned in passing in D3 on page 75, line 34, to page 76, line 8, as a hydrolysis product of interest. However, no reference to anti-HIV activity is disclosed, let alone to an enhanced potency or parent drug enrichment over the known prodrugs TD/ TDF. Therefore, the skilled person would not have been prompted by D3 to make all the selections necessary to arrive at the claimed compound (6) when seeking a solution to the posed technical problem.

10.11.3 Nor would the skilled person have been prompted to do this by common general knowledge. In fact, from D5 (pages 612 and 613, figure 1) and D48 (page 1) referred to by appellant 1, the skilled person would have merely learnt that TDF was used as a prodrug of TFV. The same information was known from, for instance, D22, D42 and D43 (point 8.1 above). However, there is no suggestion in the cited prior art that any compound of D3 that included in its structure the molecule of TFV might be used as a prodrug of TFV as alleged by appellant 1. There is also no indication in the cited prior art that it pertained to common general knowledge that the specific substituents used in the claimed compound (6) might also be used to produce a prodrug of TFV, let alone to solve the posed technical problem.

10.12 Therefore, the board comes to the conclusion that the claimed subject-matter involves an inventive step when starting from D3 as the closest prior art.

11. Thus, the subject-matter of claim 1 and claims 2 to 5 referring back to claim 1 involves an inventive step within the meaning of Article 56 EPC.

Conclusions

12. The main request of the respondent is allowable.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated