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Title of invention:
COMBINATIONS OF A PYRIMIDINE CONTAINING NNRTI WITH RT INHIBITORS

Patent Proprietor:
Janssen Sciences Ireland UC

Opponent:
Page White & Farrer Limited

Headword:
HAART regime/JANSSEN

Relevant legal provisions:
EPC Art. 83, 56
RPBA 2020 Art. 13(2)
RPBA Art. 12(4)

Keyword:

Admittance - auxiliary requests 3 and 24 (yes)
Sufficiency of disclosure - main request and auxiliary requests 1-23 (no) - auxiliary request 24 (yes)
Inventive step - auxiliary request 24 (yes)

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Case Number: T 0391/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 February 2021

Appellant: (Opponent)	Page White & Farrer Limited Bedford House John Street London Greater London WC1N 2BF (GB)
Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Respondent: (Patent Proprietor)	Janssen Sciences Ireland UC Eastgate Village, Eastgate Little Island, County Cork (IE)
Representative:	Cornish, Kristina Victoria Joy Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 December 2017 concerning maintenance of the European Patent No. 1663240 in amended form.**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	J. Molina de Alba
	R. Romandini

Summary of Facts and Submissions

I. This appeal by the opponent (appellant) lies from the opposition division's interlocutory decision that European patent No. 1 663 240 as amended according to the main request, and the invention to which it relates, met the requirements of the EPC.

Claim 1 of the main request reads as follows.

"*1. A combination comprising*

(i) 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]-amino]-benzonitrile, also named TMC278, or a stereoisomeric form thereof; or a pharmaceutically acceptable salt thereof; and

(ii) a nucleoside reverse transcriptase inhibitor and/or a nucleotide reverse transcriptase inhibitor; wherein TMC278 and the nucleotide reverse transcriptase inhibitor and the nucleoside reverse transcriptase inhibitor are therapeutically effective HIV inhibitors at a dose that can be administered once daily;

for use in the treatment of HIV infection wherein the combination is administered once daily."

II. The following abbreviations are used in this decision.

NNRTI Non-nucleoside reverse transcriptase inhibitor
NsRTI Nucleoside reverse transcriptase inhibitor
NtRTI Nucleotide reverse transcriptase inhibitor

NRTI Nucleoside or nucleotide reverse transcriptase inhibitor

III. The following documents are referred to in this decision.

D1 WO 03/016306

D2 E. De Clerk, Il Farmaco, 1999, 54, 26-45

D5 I. Frank, JAIDS, 2002, 31, S10-S15

D7 R.W. King et al., Antimicrobial Agents and Chemotherapy, 2002, 1640-6

D8 E. De Clerck, Biochimica et Biophysica Acta, 2002, 1587, 258-75

D9 British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy, HIV Medicine, 2001, 2, 276-313

D10 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services of the USA, 2003

D15 Press release, Business Wire "Gilead Initiates Study 934, a 48-Week Clinical Trial Evaluating Viread and Emtriva versus Combivir", 11 August 2003

D19 A. Pozniak et al., IAS Conference 2007, Sydney, Abstract no. WEPEA105

D20 K. Ruxrungtham et al., IAS Conference 2007, Sydney, Abstract no. TUAB105

D24 MEDLINE abstract of R. Kulkarni et al., Antiviral Res., 2014, 101, 131-5

D26 Assessment report Eviplera, European Medicines Agency, 2011

IV. The patent had been opposed on the grounds of Articles 100(a), for lack of inventive step, 100(b) and 100(c) EPC.

In the decision, the opposition division concluded, among other things, that the main request did not add subject-matter beyond the content of the application as filed and that the claimed subject-matter was sufficiently disclosed and inventive starting from any of documents D15, D5 and Dl as the closest prior art.

V. In the statement of grounds of appeal, the appellant argued that the subject-matter of the main request allowed by the opposition division was not sufficiently disclosed and not inventive starting from either of D1 and D15. The appellant requested that the decision be set aside and that the patent be revoked in its entirety.

VI. With the reply to the statement of grounds of appeal, the patent proprietor (respondent) filed the claims of a main request and 33 auxiliary requests. The main request and auxiliary requests 1-31 were identical to those filed in the opposition proceedings with the letter dated 11 November 2016.

Claim 1 of auxiliary request 1 differs from claim 1 of the main request by limitation of component (ii) to emtricitabine (**Amendment A**).

Claim 1 of auxiliary request 2 is directed to a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the combination disclosed in claim 1 of the main request (**Amendment B**).

Claim 1 of auxiliary request 3 differs from claim 1 of the main request by limitation of component (ii) to a combination of emtricitabine and a NtRTI (**Amendment C**).

Claim 1 of auxiliary request 4 differs from claim 1 of the main request by the specification that the daily dose for each of the active ingredients is between 10 mg and 300 mg (**Amendment D**).

Claim 1 of auxiliary request 5 differs from claim 1 of the main request by limitation of TMC278 to its E-isomer (**Amendment E**).

Claim 1 of auxiliary request 6 differs from claim 1 of the main request by the introduction of amendments A and B.

Claim 1 of auxiliary request 7 differs from claim 1 of the main request by the introduction of amendments A and D.

Claim 1 of auxiliary request 8 differs from claim 1 of the main request by the introduction of amendments A and E.

Claim 1 of auxiliary request 9 differs from claim 1 of the main request by the introduction of amendments B and D.

Claim 1 of auxiliary request 10 differs from claim 1 of the main request by the introduction of amendments B and E.

Claim 1 of auxiliary request 11 differs from claim 1 of the main request by the introduction of amendments D and E.

Claim 1 of auxiliary request 12 differs from claim 1 of the main request by the introduction of amendments B and C.

Claim 1 of auxiliary request 13 differs from claim 1 of the main request by the introduction of amendments C and D.

Claim 1 of auxiliary request 14 differs from claim 1 of the main request by the introduction of amendments C and E.

Claim 1 of auxiliary request 15 differs from claim 1 of the main request by the introduction of amendments A, B and D.

Claim 1 of auxiliary request 16 differs from claim 1 of the main request by the introduction of amendments A, B and E.

Claim 1 of auxiliary request 17 differs from claim 1 of the main request by the introduction of amendments A, D and E.

Claim 1 of auxiliary request 18 differs from claim 1 of the main request by the introduction of amendments B, D and E.

Claim 1 of auxiliary request 19 differs from claim 1 of the main request by the introduction of amendments B, C and D.

Claim 1 of auxiliary request 20 differs from claim 1 of the main request by the introduction of amendments B, C and E.

Claim 1 of auxiliary request 21 differs from claim 1 of the main request by the introduction of amendments C, D and E.

Claim 1 of auxiliary request 22 differs from claim 1 of the main request by the introduction of amendments A, B, D and E.

Claim 1 of auxiliary request 23 differs from claim 1 of the main request by the introduction of amendments B, C, D and E.

Claim 1 of auxiliary request 24 differs from claim 1 of the main request by limitation of component (ii) to a combination of emtricitabine and tenofovir or its prodrug tenofovir disoproxil fumarate.

VII. The board scheduled oral proceedings in line with the parties' requests. In preparation for the oral proceedings, the board issued a preliminary opinion.

VIII. Both parties replied to the board's preliminary opinion by letters dated 24 August 2020 (appellant) and 11 December 2020 (respondent).

IX. With the agreement of the parties, oral proceedings were held via videoconference on 11 February 2021.

X. The appellant's arguments, where relevant to the present decision, can be summarised as follows.

The invention in claim 1 of the main request was not sufficiently disclosed because, on the relevant date, it was not plausible that all the combinations covered by the claim were suitable for treating HIV infection

by administration once daily. The patent did not contain any data on the efficacy and safety of the claimed combinations; it only contained pharmacokinetic data of the E-isomer of TMC278 which could not even be extrapolated to the Z-isomer. It was known that drug combinations could give rise to interactions such as antagonistic effects (see D10, page 18, right-hand column, point 1, and page 22, right-hand column, paragraph 3; D5, page S14, left-column, paragraph 2) or that they could be contra-indicated for specific patient groups (see D10, page 18, right-hand column, point 2, and page 22, right-hand column, paragraph 2). Even if arguably NNRTIs and NRTIs had different binding sites (see D2, abstract) and their combinations might not be prone to show antagonism, the combinations of claim 1 included two or more NRTIs which could indeed be antagonistic to each other. Moreover, there could be interactions of other natures (see D5, page S14, left-hand column, paragraph 2). As there was no initial plausibility, post-filing evidence could not be taken into consideration. In any case, post-filing documents D19, D20 and D24 did not help because their combinations were not administered once daily. Neither did document D26, which contained data only on a very specific drug combination.

The reasons the main request did not comply with Article 83 EPC also applied to auxiliary request 3. Moreover, the respondent's argument that the subject-matter of claim 1 was extremely narrow because, to date, only two NtRTIs had been known in the art, should not be admitted. This argument had been presented for the first time at the oral proceedings before the board and constituted a change of case at a very late stage of the proceedings.

Auxiliary request 24 was inadmissible because it had not been substantiated at the outset of the appeal proceedings. The reference in the reply to the statement of grounds of appeal to the submissions made in the letter of 11 November 2016 was not adequate because these submissions did not explain the relevance of the amendment introduced in claim 1 for the issue of sufficiency of disclosure.

The reasons the invention of auxiliary request 3 was not sufficiently disclosed applied equally to the invention of auxiliary request 24.

Furthermore, the subject-matter of claim 1 of auxiliary request 24 lacked an inventive step starting from D15 as the closest prior art. It differed from the therapeutic use in D15 in that it involved the use of TCM278. As claim 1 did not exclude the use of additional NNRTIs, TMC278 could either replace or be combined with efavirenz.

The respondent had not shown that this difference led to any improvement, let alone across the whole breadth of claim 1, because it had not provided suitable comparative data. Document D26 proved (see page 47, last paragraph, and page 58, last lines) that a combination containing rilpivirine (E-TMC278) was not superior to another containing efavirenz. The former was even less efficacious in subjects with a high baseline viral load or a low CD4 T-cell count. D26 also taught (see page 59, paragraph 6) that the combination containing rilpivirine did not work at every dosage level: it was not efficacious at rilpivirine doses of 25 mg or less and not safe at doses of 50 mg or more. The same was true for emtricitabine and tenofovir, as derivable from the patent (see paragraph [0035], last

line, and paragraph [0040], last line). However, claim 1 did not contain any limitation in terms of doses. Furthermore, the data on file related to E-TMC278; there was no evidence on Z-TMC278. Hence, the objective technical problem was the provision of an alternative combination suitable for administration to HIV patients once daily.

The problem as formulated by the respondent in terms of a reduction of pill burden was not solved by the use in claim 1 because the claim had an open language and covered combinations containing efavirenz.

The treatment proposed in claim 1 would have been an obvious solution. Starting from D15, the skilled person would have either (i) replaced efavirenz with TMC278 or (ii) added TMC278.

Regarding option (i), the replacement of efavirenz with another NNRTI was necessary in some instances because efavirenz was known to cause resistance and to be teratogenic (see D9, page 285, right-hand column, last paragraph, to page 286, left-hand column, first paragraph; and D10, page 22, right-hand column, paragraph 2) or because it could not achieve optimum effects (see D5, page S14, left-hand column, paragraph 2). In the search for alternative NNRTIs, the skilled person would have found TMC278, which was one of the preferred compounds in D1 (see compound 1 on page 18, paragraph 2, and page 67, Example B) and had an excellent antiretroviral efficacy (see Table 6 on page 103). Although D1 did not explicitly disclose that TMC278 was suitable for once-daily administration, this was not excluded, and its suitability would have been found by routine testing. In any case, it was common general knowledge that once-daily administration would

become the standard of care for the treatment of HIV infection (see D5, last paragraph), and that any drug could be formulated in a way that allowed once-daily administration as a routine operation. Thus, replacing efavirenz with TMC278 would have resulted from a try-and-see approach without involving more than routine testing.

As to option (ii), the skilled person would have added TMC278 to the combinations of D15 to reduce the resistance potentially arising from efavirenz and to enhance the efficacy of the combination.

XI. The respondent's arguments, where relevant to the present decision, can be summarised as follows.

The invention in claim 1 of the main request was sufficiently disclosed. The evidence in the patent examples made plausible that the once-daily administration of the combinations defined in claim 1 was suitable for reducing or maintaining at low levels the HIV load in a patient. Example 1 showed that the E-isomer of TMC278 was safe at different doses and that it had a half-life in plasma greater than 37 hours. Example 2 showed that, *in vitro,* E-TMC278 was more effective and better reduced the emergence of HIV resistance than the reference NNRTIs nevirapine and efavirenz. It also contained safety data (see paragraph [0104]). Post-published documents D19, D20 and D24 provided additional evidence included in the assessment report from the European Medicines Agency D26. Regarding the breadth of claim 1, the antiviral activity of the Z-isomer of TMC278 was similar to that of the E-isomer (see Table 1 of the patent), and the number of combinations encompassed by claim 1 was very limited because the active ingredients of component

(ii) had to be effective HIV inhibitors at a dose that could be administered once daily (see D5, page S12, Table 3). Thus, the skilled person would have had to carry out only a limited number of tests to find suitable combinations and their doses. In this context, on the relevant date, the standard of care for the treatment of HIV was the combination of one NNRTI with one or more NRTIs. No antagonism had been shown between NNRTIs and NRTIs because they bound to distinct sites (see D2, abstract); the antagonism mentioned in D10 (see page 22, paragraph 3) concerned zidovudine and stavudine, i.e. NRTIs which were not effective HIV inhibitors when administered once daily and therefore not covered by claim 1. In conclusion, the appellant had not discharged its burden to raise serious doubts substantiated by verifiable facts.

The subject-matter of claim 1 of auxiliary request 3 was sufficiently disclosed. It was considerably narrower and closer to the post-filing evidence in D26 than the main request because, to date, only two NtRTIs were known in the art, namely tenofovir and tenofovir disoproxil fumarate. Therefore, auxiliary request 3 met the requirement of sufficiency of disclosure.

Auxiliary request 24 had to be admitted into the appeal proceedings because it had been filed in the opposition proceedings with the letter of 11 November 2016. The letter explained (page 32, section "Amendment F") the origin of the amendment introduced in claim 1 and the impact that it had on the issue of inventive step. The explanation was still relevant at the outset of the appeal proceedings because the opposition division had allowed the main request and had not decided on the auxiliary requests. It was self-evident how the

amendment also affected the issue of sufficiency of disclosure.

For the reasons put forward in relation to auxiliary request 3, auxiliary request 24 also complied with the requirements of Article 83 EPC.

In addition, the subject-matter of claim 1 of auxiliary request 24 was inventive. It differed from the therapeutic use disclosed in the closest prior art (D15) in that the NNRTI was TMC278 rather than efavirenz. The combination of claim 1 was not only as efficacious as that in D15, it also had reduced adverse effects and pill burden. This was demonstrated in the patent and in D26: the patent showed (see Tables 1 and 5 and paragraphs [0102] and [0103]) that E-TMC278 and Z-TMC278 exhibited similar anti-HIV efficacy and that they were superior to efavirenz; D26 proved (see page 37, section "Objectives"; page 47, last paragraph; page 60, paragraph 3 from the bottom; page 61, last paragraph; page 62, paragraph 1; page 66, paragraph 6; page 85, paragraph 3; and page 88, paragraph 3) non-inferiority and a lower level of adverse effects for a composition according to claim 1 containing 25 mg TMC278 as the NNRTI, compared with the same composition containing 600 mg efavirenz as the NNRTI.

Thus, in line with the teaching in the patent (see paragraphs [0009], [0012], [0094], [0095] and [0098], and Tables 1 and 5), the objective technical problem was the provision of an anti-HIV therapy for once-daily administration which had higher potency, a lower level of adverse effects and reduced pill burden.

The solution proposed in claim 1 would not have been obvious. Firstly, the skilled person could have

modified the combinations in D15 in several ways, not just by replacing the NNRTI. In fact, the clinical trials in D15 kept efavirenz constant and modified the NRTIs. Secondly, even if the skilled person would have sought to modify the NNRTI, D1 did not provide a reasonable expectation that TMC278 was suitable for once-daily administration; it did not contain pharmacokinetic data and suggested (see page 50, lines 33-35) administration two or more times daily. In this context, the appellant's submission that any drug could be formulated for once-daily administration was unfounded and fundamentally flawed. If the skilled person would have wanted to replace the NNRTI, they would have chosen another type of antiretroviral drug rather than an alternative NNRTI, as is generally made in the development of anti-HIV therapy (see D8, abstract).

XII. The parties' final requests were the following.

- The appellant requested that the appealed decision be set aside and that the patent be revoked in its entirety. It also requested that auxiliary requests 1-33, filed by the respondent with its reply to the statement of grounds of appeal, not be admitted into the appeal proceedings.

- The respondent requested that the appeal be dismissed, implying that the patent be maintained in the version considered allowable by the opposition division (main request). Alternatively, it requested that the patent be maintained in amended form on the basis of any of the sets of claims of auxiliary requests 1-33, filed with the reply to the statement of grounds of appeal.

XIII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. Main request - sufficiency of disclosure

2.1 Claim 1 of the main request is directed to a combination of active ingredients for treating HIV infection in a regime of once-daily administration. The claim contains the following two requirements: (i) the combination of active ingredients must be suitable for treating HIV infection when administered once daily and (ii) each of the individual active ingredients must be therapeutically effective HIV inhibitors at a dose that can be administered once daily.

Under these circumstances, what the expressions "treating HIV infection" and "therapeutically effective HIV inhibitor" mean needs to be established first. It was not disputed that, in line with paragraphs [0024], [0064] and [0073] of the patent, "treating HIV infection" means inhibiting or suppressing HIV infection or, as expressed by the respondent, reducing HIV load or maintaining it at low levels to prolong the patient's survival. Similarly, a "therapeutically effective HIV inhibitor" is a compound which reduces or maintains the patient's viral load at low levels.

It is common general knowledge that the therapeutic effectiveness of a treatment not only depends on the

nature of the active ingredients but also on its dosage regime, i.e. the amounts and times at which the active ingredients are administered to the patient. Thus, it follows from the wording of claim 1 that the examination of sufficiency of disclosure boils down to assessing whether, at the filing date of the patent, the skilled person could have found the following without undue burden:

(a) the once-daily dose at which TMC278 reduces or maintains the patient's HIV load at a low level
(b) specific NRTIs and their doses which reduce or maintain the patient's HIV load at a low level when administered once daily
(c) combinations of TMC278 with at least one of these NRTIs, and their corresponding doses, suitable for reducing or maintaining the patient's HIV load at a low level when administered once daily

2.2 Regarding point (a), the patent indicates in paragraph [0008] that TMC278 is one of the NNRTIs disclosed in document D1 (see compound 1 on page 67 and Table 6 on page 103). It also contains *in vitro* evidence on the virological profile of the E-isomer of TMC278 against wild type and mutant HIV and on its ability to prevent HIV infection via intimate contact between partners (see Examples 2-3). E-TMC278 appeared to be considerably more effective (see lower IC50 values in Table 5) than the commercially available NNRTIs nevirapine and efavirenz. In addition, albeit less effective than the E-isomer, the Z-isomer of TMC278 was still more effective than nevirapine and efavirenz (see Tables 1 and 5).

Moreover, the patent describes (see Example 1) the results of two phase I studies in which E-TMC278 had

been administered at oral doses of 12.5, 25, 50, 100 and 200 mg to healthy male subjects. They show that E-TMC278 was well tolerated and that its half-life in plasma ranged between 37 and 39 hours (see Table 4).

Thus, at the filing date, the patent application had made credible that E-TMC278 was suitable for treating HIV infection by once-daily administration and had provided a workable dose range.

Although the half-life data of E-TMC278 cannot be directly extrapolated to its Z-isomer, taking into consideration the extreme structural similarity of the two compounds, their close biological behaviour in terms of antiretroviral activity (see Table 1 of the patent), and the fact that E-TMC278 has a half-life far beyond 24 hours, there are no serious doubts that Z-TMC278 also has a pharmacokinetic profile suitable for treating HIV infection by once-daily administration.

Hence, at the filing date, the patent application would have made it credible for the skilled person that TMC278 was suitable for reducing or maintaining at a low level a patient's HIV load when it was administered once daily. The dose range for achieving this result was also provided in the application as filed.

2.3 With regard to point (b), at the filing date, several NRTIs had already been approved for once-daily administration, and some others were in development (see document D5, Table 3). In consequence, the skilled person would have had no undue burden to find NRTIs that were effective HIV inhibitors at a dose that can be administered once daily.

2.4 Regarding point (c), the patent does not contain any evidence on combinations of TMC278 with NRTIs. Thus, whether the skilled person would have been able to find suitable combinations and their respective doses without undue burden needs to be assessed on the basis of the common general knowledge.

2.4.1 As noted by the appellant (see statement of grounds of appeal, point 5.1.1, paragraph 1, and the conclusion), at the filing date, it was common practice to use double and triple combinations of antiretroviral drugs to treat HIV infection. Conventional drug cocktails to prevent the emergence of drug-resistant HIV strains were combinations of one NNRTI with two NRTIs. This common general knowledge was reflected for instance in the review document D8 (see page 259, left-hand column, paragraph 1), the guidelines D9 (see Table 3, recommended regimen) and D10 (see page 14, right-hand column, paragraph 3, and page 51, Table 12a).

In view of this common general knowledge, it would have been plausible that the combination of TMC278 with one or more NRTIs known to be therapeutically effective HIV inhibitors when administered once daily could be effective for treating HIV infection by once-daily administration.

2.4.2 However, this initial plausibility cannot be equated with meeting the requirement of Article 83 EPC. It is basic knowledge in the field of pharmaceutical combinations that in the absence of experimental data (or previous related knowledge), the interaction between individual active ingredients at physiological levels is unpredictable; the compatibility of the ingredients and the suitability of their combinations for the envisaged treatment at given doses needs to be

assessed *in vivo*. The higher the number of combined active ingredients, the more complex becomes the situation and the higher the likelihood of undesirable interactions. The case of antiretroviral combinations and their once-daily administration is not an exception. Indeed, review document D5 (page S14, left-hand column, paragraph 2, emphasis added by the board) states:

"***Not all drugs that are potentially available as once-daily agents can be assembled into a once-daily combination.*** *Food restrictions may require some drugs to be taken in a staggered fashion. For example, it is recommended that didanosine and efavirenz be taken on an empty stomach, whereas tenofovir and lopinavir/ ritonavir should be taken with food. Also,* ***there are pharmacokinetic interactions*** *between didanosine and tenofovir; tenofovir boosts didanosine concentrations.* ***Such drug-drug interactions require further evaluation to establish the appropriate doses of these drugs when administered together.***"

It was also known from the guidelines in D10 (page 20, left-hand column, paragraph 2, emphasis added by the board) that:

"*Potential drug-drug interactions should be taken into consideration*" and "***review of drug interaction potential should be undertaken when any new drug is to be added to an existing antiretroviral combination***."

D10 also noted on page 22 (right-hand column, paragraph 3) that the NRTIs zidovudine and stavudine should not be combined because they had been shown to be antagonistic.

2.4.3 The existence of an initial plausibility nevertheless allows the board to consider post-published evidence which fills the probative gap that existed at the filing date. In this context, the respondent referred to the clinical trials in documents D19, D20, D24 and D26. It nevertheless indicated at the oral proceedings before the board that the evidence in D19, D20 and D24 was contained in D26. Hence, the content of the former documents does not need to be discussed in this decision; the board will refer to D26 only.

Document D26 is the assessment report for authorisation by the European Medicines Agency (EMA) of Eviplera®. Eviplera® is a film-coated tablet to be administered once daily for the treatment of HIV infections. It contains 200 mg emtricitabine, 25 mg rilpivirine and 245 mg tenofovir disoproxil fumarate (see D26, pages 2-3 and page 10, last paragraph). Rilpivirine is the E-isomer of TMC278 (see D26, page 11, Figure 1), emtricitabine is a NsRTI (see D26, page 12, Figure 2) and tenofovir disoproxil fumarate is a NtRTI (see D26, page 13, Figure 3). In view of the available evidence, the EMA committee decided to recommend the granting of a marketing authorisation for the requested use of Eviplera® (see D26, page 89, title "Outcome").

2.4.4 D26 proves that the skilled person could have carried out the treatment of claim 1 to the extent that it concerned the combination of E-TMC278 with emtricitabine and tenofovir disoproxil fumarate. However, this appears insufficient to make credible that every possible combination of TMC278 with NRTIs that are therapeutically effective by once-daily administration would be suitable for treating HIV in a once-daily dosage regime. To find suitable combinations and their corresponding doses among all the

possibilities covered by claim 1, the skilled person would have needed to carry out an undue amount of research. As explained above, drug-drug interactions need to be assessed for each drug combination to find whether and at which dose the combination is therapeutically effective. Such an assessment involves clinical studies which cannot be considered routine tests. Even if, as argued by the respondent, the number of NRTIs suitable for once-daily administration were not particularly high (see D5, Table 3), the research required would go far beyond what may be seen as routine testing.

2.5 Therefore, there exist serious doubts substantiated by verifiable facts that the skilled person could have carried out the treatment of claim 1 across its whole breadth without undue burden. As these doubts were not removed by the respondent, the main request does not meet the requirement of Article 83 EPC.

3. Auxiliary request 3 - admittance

In view of the outcome of the assessment of sufficiency of disclosure in relation to this request (see point 4), the board sees no need to provide reasons for its decision to admit the request into the proceedings.

4. Auxiliary request 3 - sufficiency of disclosure

4.1 In claim 1 of auxiliary request 3, the combination of claim 1 of the main request was restricted by specifying that component (ii) is a combination of emtricitabine and a NtRTI.

4.2 At the oral proceedings before the board, the respondent alleged for the first time that claim 1 was

in fact restricted to a combination of TMC278, emtricitabine and tenofovir or its prodrug tenofovir disoproxil fumarate because to date tenofovir and tenofovir disoproxil fumarate were the only NtRTIs known in the art. This alleged fact constituted a change to the respondent's case at a late stage of the proceedings. However, the respondent did not justify by cogent reasons that there were exceptional circumstances to take the new alleged fact into consideration. Hence, the board disregarded the alleged fact pursuant to Article 13(2) RPBA 2020.

4.3 Having regard to the evidence in D26, claim 1 still covers more combinations and doses than could have been carried out without an undue amount of testing. Therefore, the reasons of insufficiency explained in relation to the main request (see point 2.4 above) remain valid, and auxiliary request 3 is contrary to Article 83 EPC.

5. Auxiliary requests 1, 2 and 4-23 - sufficiency of disclosure

The respondent did not put forward any additional arguments specifically directed to these requests.

Without prejudice to the issue of their admittance, auxiliary requests 1, 2 and 4-23 are contrary to Article 83 EPC for the reasons explained in relation to the main request and auxiliary request 3. This is apparent from the fact that:

- like the main request, auxiliary requests 2, 4, 5, 9-11 and 18 contain claims directed to the combination of TMC278 with two unspecified NRTIs; and

- like auxiliary request 3, auxiliary requests 1, 6-8, 12-17 and 19-23 contain claims directed to the combination of TMC278 with emtricitabine and an unspecified NtRTI.

6. *Auxiliary request 24 - admittance*

The respondent had filed auxiliary request 24 in the opposition proceedings with the letter dated 11 November 2016. It re-filed the request with the reply to the statement of grounds of appeal and referred to the submissions made in that letter.

In the appellant's view, the reference to the submissions in the opposition proceedings did not fulfil the requirements of Article 12(2) RPBA 2007. Therefore, the request had to be held inadmissible under Article 12(4) RPBA 2007.

In the letter of 11 November 2016, the respondent indicated (page 32, section "Amendment F") that claim 1 of auxiliary 24 constituted a further narrowing of claim 1 of auxiliary request 3; it was identical to claim 10 as granted and claim 11 as filed. The letter also explained the impact of this amendment on the issue of inventive step. Albeit not explained in the letter, it was apparent that the amendment in claim 1 made the claimed subject-matter even closer to the post-filing evidence submitted in the context of sufficiency of disclosure (i.e. D19, D20 and D24).

In the appealed decision, the opposition division concluded that the patent could be maintained on the basis of the main request. Thus, the submissions regarding inventive step in relation to auxiliary request 24 in the opposition proceedings remained

relevant at the outset of the appeal proceedings and potentially addressed the lack of inventive step objections raised by the appellant in the statement of grounds of appeal. It was also apparent that the amendment introduced in claim 1 of auxiliary request 24 made the claimed subject-matter narrower and closer to the post-filing evidence which had been filed in the context of the issue of sufficiency of disclosure.

Therefore, the board decided to admit auxiliary request 24 into the proceedings (Article 12 (2) and (4) RPBA 2007).

7. *Auxiliary request 24 - sufficiency of disclosure*

Claim 1 of auxiliary request 24 corresponds to claim 1 of the main request with the limitation that the combination comprises TMC278, emtricitabine and tenofovir or its prodrug tenofovir disoproxil fumarate. This amendment narrows the claimed subject-matter to encompass only the combination tested in D26 and some very closely related combinations. The skilled person wanting to carry out the invention would have had to find which of the active ingredient combinations covered by claim 1 and at which doses were suitable for treating HIV infections in a once-daily administration regime. Claim 1 covers variations in three respects:

- The NNRTI may be E-TMC278 or Z-TMC278.
- The NtRTI may be tenofovir or its prodrug tenofovir disoproxil fumarate.
- The doses may be modified.

D26 showed that a combination according to claim 1 containing 200 mg emtricitabine, 25 mg E-TMC278 and

245 mg tenofovir disoproxil fumarate was suitable for treating HIV infections when administered once daily.

Regarding the NNRTI, the board explained above (point 2.2, paragraph 4) that compound Z-TMC278 could have been expected to have a physiological behaviour similar to E-TMC278. So it may be reasonably assumed that a combination containing Z-TMC278 instead of E-TMC278 would also have been suitable for treating HIV infections by once-daily administration at doses close to those disclosed for E-TMC278.

Regarding the NtRTI, tenofovir disoproxil fumarate is the prodrug of tenofovir, so both active ingredients may be expected to have similar properties in terms of therapy and interactions. The appellant did not raise any objection in this respect. Therefore, the board has no serious doubts that tenofovir is also a suitable NtRTI for the treatment of claim 1.

On the third point, the skilled person would have had a clear orientation on the range within which the suitable dose of the active ingredients could vary. This could be found in Table 2 in the patent, which illustrates dose examples for combinations containing E-TMC278, emtricitabine and tenofovir. Table 4 also shows suitable doses of E-TMC278, and a similar range could be assumed for Z-TMC278. Furthermore, suitable doses of emtricitabine, tenofovir and tenofovir disoproxil fumarate were generally known at the filing date since they were all commercially available NRTIs for the treatment of HIV infections.

Hence, the board concludes that, considering the evidence in D26 that a combination containing E-TMC278, emtricitabine and tenofovir disoproxil fumarate

effectively treats HIV infections by once-daily administration, it could have been expected that related combinations where the NNRTI was Z-TMC278 or the NtRTI was tenofovir were suitable as well. In addition, the skilled person would have had sufficient information from the patent and the common general knowledge to find suitable doses for each of the active ingredients without undue burden. Thus, auxiliary request 24 meets the requirement of Article 83 EPC.

8. Auxiliary request 24 - inventive step

8.1 At the oral proceedings before the board the parties concurred that document D15 was the most promising starting point for the assessment of inventive step in relation to claim 1 of auxiliary request 24. The board sees no reason to take another stance.

Document D15 is a press release announcing the initiation of a comparative phase III study to assess the efficacy of a combination containing 600 mg efavirenz, 200 mg emtricitabine (Emtriva™) and 300 mg tenofovir disoproxil fumarate (Viread®) for treating HIV infection in a once-daily administration regime.

8.2 The board concurs with the respondent that the treatment of claim 1 differs from the one proposed in D15 in that the NNRTI component is TMC278 rather than efavirenz.

The appellant argued that the difference was not that the combination of claim 1 contained TMC278 instead of efavirenz but only that it contained TMC278. This resulted from the fact that the combination of claim 1 was defined with an open wording (comprising) and was

not limited to the active ingredients explicitly mentioned, i.e. it could also contain efavirenz.

In this respect, the board notes that the problem-solution approach is a tool for assessing the patent contribution over the prior art. This contribution can only be reasonably assessed on the basis of the features essential to the invention. The fact that optional ingredients could be added is irrelevant in this respect and should not be considered for establishing the difference with the closest prior art and formulating the objective technical problem. According to claim 1, the only active ingredient essential in the NNRTI component is TMC278. Non-essential NNRTIs, such as efavirenz, should not be considered for the formulation of the objective technical problem, even if they could optionally be added. This might nevertheless become relevant at a later stage, namely in the assessment of obviousness.

8.3 For determining the effect that the difference brings about, the parties referred to document D26. This document disclosed the results of a phase III clinical test designated as C209 (see page 32, Figure 4; page 36, paragraph 2; and page 37, paragraph 1) which compared two treatments of HIV infection that were administered once daily. In the first treatment, the active ingredient combination consisted of 25 mg E-TMC278 (rilpivirine, RPV), 200 mg emtricitabine and 245 mg tenofovir disoproxil fumarate (see pages 2-3 and page 10, last paragraph). In the second, the 25 mg E-TMC278 had been replaced with 600 mg efavirenz (EFV). The primary objective of C209 was to show the non-inferiority of the treatment with 25 mg E-TMC278 compared to 600 mg efavirenz (see page 37, paragraph 3, and page 46, last full paragraph). The objective was

fulfilled because the treatment with E-TMC278 showed an efficacy not superior but comparable to that with efavirenz (see page 47, last paragraph; page 48, paragraph 1; page 60, section 2.5.4, paragraph 1; and page 88, paragraph 3). Furthermore, the treatment was generally safe and well tolerated; it was at least at the level of the efavirenz treatment (see page 61, title "Adverse events", to page 62, paragraph 1; page 66, paragraph 6; and page 85, paragraph 3).

In short, D26 showed that a treatment according to claim 1, in which the NNRTI (E-TMC278) is administered at a dose of 25 mg, is equivalent in terms of efficacy and safety to a treatment as disclosed in D15, in which the NNRTI (efavirenz) is administered at a dose of 600 mg. It is therefore apparent that the treatment according to claim 1 involves a considerably lower pill burden than the one of the closest prior art. This effect may also be expected for combinations comprising Z-TMC278 since, as shown in Tables 1 and 5 of the patent, Z-TMC278 is slightly less active than E-TMC278, but its activity remains in the same order and well above that of efavirenz.

In this context, the appellant argued that an equivalent efficacy and safety with lower pill burden could not be expected for all the claimed treatments because claim 1 did not indicate any dose and was open to the addition of further components. On the first point, the board notes that claim 1 requires that the therapy be effective, i.e. that it reduces viral load or maintains it at lower levels. This condition implicitly imposes dose ranges, as explained in the context of sufficiency of disclosure. D26 proves that a combination of TMC278, emtricitabine and tenofovir disoproxil fumarate has a considerably reduced pill

burden compared to a therapeutically equivalent combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. The argument that there might possibly be combinations with doses according to claim 1 that would not be therapeutically equivalent and not have reduced pill burden with regard to the closest prior art is an unfounded allegation. On the second point, the fact that claim 1 has an open wording cannot be interpreted in an unreasonable manner to consider that the skilled person would have added components which do not contribute to the therapy but which increase pill burden.

8.4 Based on the above, the board concludes that, in line with the indications in the patent in paragraphs [0003], [0009] and [0012], the objective technical problem is the provision of an effective and safe treatment of HIV infection in a once-daily administration regime, where the treatment has reduced pill burden.

The board is satisfied that the subject-matter of claim 1 solves the problem.

8.5 On the issue of obviousness, the appellant submitted that the skilled person would have arrived at the subject-matter of claim 1 by two possible, obvious ways. Firstly, by replacing efavirenz with E-TMC278 in the treatment of D15. Secondly, by adding TMC278. In this context, the appellant cited document D1, which discloses the family of NNRTIs that includes TMC278 (compound 1).

The board does not dispute that the skilled person could have contemplated replacing efavirenz, at least partially, with another NNRTI as one of the possible

solutions. Nevertheless, to have expectations of success, the new NNRTI would have had to be known to be effective against HIV when administered once daily at doses lower than efavirenz and to not produce negative interactions with emtricitabine and tenofovir. At the filing date, this information was not available in relation to the NNRTIs of D1, let alone in relation to TMC278. Firstly, there were no pharmacological data showing that the compounds of D1 would be effective when administered once daily, and D1 suggested (page 50, lines 33-35) administration two, three, four or more times a day. In this respect, the appellant's allegation that any active ingredient may be formulated routinely for once-daily administration is not supported by evidence. Secondly, there were no efficacy data available which could be directly compared with those of efavirenz to show that the compounds of D1, and TMC278 in particular, had an equivalent antiretroviral effect at lower doses. Thirdly, there were no data available showing that the NNRTIs of D1 were compatible with emtricitabine and tenofovir for once-daily administration.

Regarding the appellant's argument that the skilled person would have added TMC278 to the combination of D15 rather than replacing efavirenz, it is apparent that the skilled person would not have done so to reduce pill burden since this would have had exactly the opposite effect.

In conclusion, the board holds that the subject-matter of claim 1 of auxiliary request 24 is inventive and complies with Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the following documents:

   - claims 1-11 of auxiliary request 24 filed with the reply to the statement of grounds of appeal, dated 14 September 2018;

   - a description to be adapted.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated