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Datasheet for the decision of 13 March 2025

Case Number: T 0355/23 - 3.3.07

Application Number: 16798063.0

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Language of the proceedings: EN

Title of invention:
THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Patent Proprietor:
Gilead Sciences, Inc.

Opponents:
Teva Pharmaceutical Industries Ltd.
Cooke, Richard
Sandoz GmbH

Headword:
Fixed-dose combination against HIV/GILEAD

Relevant legal provisions:
EPC Art. 123(2), 54(3), 56
RPBA 2020 Art. 12(4), 12(6)

Keyword:

Amendments - allowable (yes)
Novelty - (yes)
Inventive step - (yes)

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Case Number: T 0355/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 13 March 2025

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 December 2022 concerning maintenance of the European Patent No. 3346995 in amended form**

Composition of the Board:

Chairman A. Usuelli
Members: J. Molina de Alba
L. Basterreix

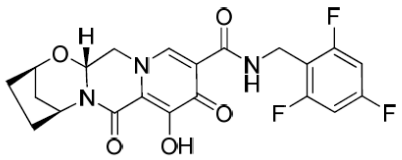
Summary of Facts and Submissions

I. The decision under appeal is the opposition division's interlocutory decision rejecting the main request and concluding that the European patent as amended according to auxiliary request 1, and the invention to which it relates, met the requirements of the EPC.

Claims 1 and 8 of the main request on which the decision is based read as follows:

"*1. A tablet comprising 50 mg of the compound of Formula I:*

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof."

"*8. A tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.*"

The compound of Formula I is commonly known as bictegravir.

II. The following documents are mentioned in the present decision:

D1 WO 2015/196116 A1

D3 WO 2014/100323 A1

D5 WO 2015/022351 A1

D7 British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015, September 2015, 12-14

D18 WHO Drug Information, 29(2), 2015, 195-301

D36 Biktarvy assessment report, European Medicines Agency, 28 April 2018, 1-104

D50 I. Song et al., Antimicrobial Agents and Chemotherapy, 56(3), 2012, 1627-9

III. In the decision under appeal, the opposition division found that the tablet defined in claim 1 of the main request added subject-matter. With regard to auxiliary request 1, the opposition division noted that no added subject-matter objections had been raised. It then concluded that the tablet in claim 1 of auxiliary request 1 was novel over D1 and inventive starting from D5 as the closest prior art.

IV. Each of the patent proprietor and opponents 1 to 3 filed an appeal against the decision. As each party is both appellant and respondent, they will be referred to below as patent proprietor and opponents 1 to 3.

V. In its statement of grounds of appeal, the patent proprietor requested that the opposition division's decision be set aside and that the patent be maintained in amended form on the basis of the main request on which the decision is based, which was filed on 26 August 2022. Alternatively, the patent proprietor requested that the patent be maintained in amended form on the basis of one of auxiliary requests 1 to 10, all filed on 26 August 2022.

VI. In their statements of grounds of appeal, the opponents requested that the opposition division's decision be set aside and that the patent be revoked in its entirety. Opponent 3 filed five documents, including D50.

VII. With its reply to the opponents' statements of grounds of appeal, the patent proprietor filed eight additional documents.

VIII. The board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

IX. Oral proceedings were held before the board. At the end of the oral proceedings, the board announced its decision.

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

Amendments

Claim 1 of the main request was an allowable generalisation of claim 7 as filed in that the claimed tablet was not limited to a coated tablet. This generalisation was directly and unambiguously derivable from a general reading of the application as filed which taught that the tablet coating was not inextricably linked with the other features in claim 7 as filed. Paragraph [0071] and claims 6 and 9 as filed supported this view. Paragraph [0071] generally stated that coating of the tablet was optional. The tablets disclosed in claims 6 and 9 as filed contained the active ingredients of claim 7 but were not coated. The generalisation in claim 1 of the main request did not

present the skilled person with new technical information and met the gold standard. Other relevant disclosures in the application as filed could be found in paragraphs [0010], [0016] and [0053], and claims 8 and 11.

Novelty

D1 did not disclose a tablet as in claim 1 of the main request because multiple selections had to be made to arrive at it. These included the selection from paragraph [0096] of the embodiment disclosing the combination of sodium bictegravir with 25 mg tenofovir alafenamide and 200 mg emtricitabine, and the embodiment that the sodium bictegravir dose was 50 mg. In addition, a fixed-dose tablet had to be selected from paragraph [0065] or claim 21 and combined with the selections from paragraph [0096]. D1 did not contain any pointer for those selections.

Inventive step

The embodiment in the passage bridging pages 19 and 20 of D5 was not suitable closest prior art as it fell outside the invention of D5, which was characterised by a weight ratio dolutegravir to emtricitabine of 1:1 to 1:3. Furthermore, D5 did not contain any data showing that the selected embodiment was safe and effective for treating HIV infection.

If the embodiment selected by the opponents was nevertheless taken as the closest prior art, the subject-matter of claim 1 differed in that the formulation was a fixed-dose tablet containing the three active ingredients and in that the integrase inhibitor was bictegravir instead of dolutegravir. The

examples in the patent, especially Example 9, demonstrated that the claimed combination of active ingredients was safe and effective for treating HIV infection and that it could be administered without regard to food intake. These technical effects were never contested by the opponents and they were also confirmed by the EMA in D36. Therefore, the objective technical problem was the provision of a combination therapy which is effective for the treatment of HIV in humans and provides near-maximal virologic response and minimised food effects.

The solution proposed in claim 1 was not obvious. The skilled person had no motivation to solve the objective technical problem by replacing dolutegravir with bictegravir, keeping the same dose and selecting a tablet as the dosage form. D5 disclosed combinations containing dolutegravir, tenofovir and emtricitabine but did not contain any experimental data for the combination selected as the closest prior art. D5 contained no evidence showing that the combination in the passage bridging pages 19 and 20 was safe and effective for treating an HIV infection in humans. There was also no teaching in D5 to replace dolutegravir instead of tenofovir or emtricitabine. The solution proposed in D5 was to modify the weight ratio of dolutegravir to emtricitabine to within the range 1:1 to 1:3. In any case, the skilled person could have no expectation of solving the objective technical problem because D5 contained only *in vitro* data. It could not be expected that, *in vivo*, the fixed-dose combination disclosed in claim 1 would deliver useful concentrations of each of the active ingredients, let alone independently of food intake.

Even if, contrary to the teaching of D5, the skilled person did consider replacing dolutegravir, the list of alternative anti-HIV drugs suggested in D7 did not include bictegravir. The latter was not an established therapy against HIV infection - it was not even an approved drug. The skilled person would not have turned to the unknown integrase inhibitors disclosed in D3 to replace dolutegravir. Even less would they have selected bictegravir out of the numerous examples in D3. Therefore, it was unrealistic that the skilled person would simply exchange 50 mg dolutegravir with 50 mg bictegravir in the combination of the closest prior art and expect to solve the objective technical problem.

The opponents' approach was tainted with hindsight because it focused on selected information in D5 and D7 ignoring the main teaching of these documents. In particular, the opponents ignored the weight ratios of dolutegravir to emtricitabine that constituted the core of the invention in D5 and the alternatives to dolutegravir proposed in D7.

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

Amendments

The standard of disclosure for assessing added subject-matter was the gold standard rather than whether the claimed subject-matter was obvious when reading the application as filed. Claim 1 of the main request was an unallowable generalisation of either claim 7 or paragraph [0008] as filed. Claim 6 as filed was broader than claim 7; it did not disclose the amounts of active ingredients nor that the tablet was coated. Those

amounts and the tablet coating were linked in claim 7 and could not be uncoupled. Embodiments in other claims as filed, such as claims 8, 9 and 11, were specific and could not be used to broaden claim 7 as filed. Paragraph [0071] did not help either. It stated that the tablets of the invention could be coated or uncoated, but the tablet of claim 7 as filed was unambiguously coated.

Similarly, the embodiment in paragraph [0008] of the application as filed was specific and limited to emtricitabine being the third active ingredient. This embodiment could not be broadened by including pharmaceutically acceptable salts of emtricitabine just because there were embodiments in the application as filed that contained those salts.

The limitations in the specific embodiments of the application as filed were not accidental but deliberate, meaning that the embodiments could not be arbitrarily combined and broadened.

Novelty

Paragraph [0096] of D1 disclosed in one embodiment the combination of 50 to 500 mg sodium bictegravir with 25 mg tenofovir alafenamide and 200 mg emtricitabine. The most preferred formulation in D1 was a fixed-dose tablet since it was the only formulation claimed. This was derivable from paragraph [0065], the section relating to combination therapy, especially paragraph [0081], and claims 13 and 21. Therefore, the embodiment disclosed in paragraph [0096] was a fixed-dose tablet containing the three active ingredients. This meant that only one selection had to be made to arrive at the tablet in claim 1 of the main request, namely that

sodium bictegravir was present in an amount of 50 mg. Therefore, the claimed tablet was not novel.

Inventive step

The embodiment in the passage bridging pages 19 and 20 of D5 was disclosed as being preferred and could be cited as the closest prior art. Whether this embodiment was in accordance with claim 1 of D5 was irrelevant. For instance, Table 1 of D5 illustrated an active ingredient combination with excellent antiretroviral activity which was not in accordance with claim 1 of D5. The combination contained the amounts of dolutegravir and emtricitabine disclosed in the embodiment bridging pages 19 and 20. This closest prior art was in line with the common general knowledge in Table 5.1 of D7 that the gold standard for treating an HIV infection was a combination therapy containing a backbone of tenofovir and emtricitabine and a third antiretroviral drug, such as the integrase inhibitor dolutegravir. Therefore, it was credible that the combination of the closest prior art was suitable for treating an HIV infection. In addition, the most preferred dosage form in D5 was a tablet.

The tablet in claim 1 of the main request differed from the closest prior art in that the integrase inhibitor was bictegravir instead of dolutegravir.

There was no evidence on file showing a technical effect in comparison with the closest prior art. Therefore, no technical effect could be attributed to the distinguishing technical feature. The objective technical problem was the provision of an alternative tablet for treating HIV infection.

The solution proposed in claim 1 was obvious. The combination of tenofovir with emtricitabine at the doses defined in claim 1 was the standard backbone for treating HIV infection. Dolutegravir was a new generation integrase inhibitor and its combination with tenofovir and emtricitabine had also become standard therapy at the filing date (D7, Table 5.1). In addition, D3 suggested replacing dolutegravir with bictegravir.

D3 disclosed bictegravir (compound 42) as a promising HIV integrase inhibitor. It had shown an excellent antiretroviral activity *in vitro* (Example 104), was one of the few compounds for which phamacokinetics had been tested in beagle dogs (Example 107) and was one of the few compounds claimed (claim 32). Furthermore, an international non-proprietary name had been requested before the World Health Organisation (D18). Therefore, the skilled person was aware that bictegravir was at an advanced stage of clinical development and that it was a suitable alternative to dolutegravir in the combination of the closest prior art. Finding the required dose for bictegravir or formulating the three active ingredients into a fixed-dose combination tablet was a matter of routine. A reduced food effect of bictegravir could also be expected since it was known that a dolutegravir dose of 50 mg could be taken without regard to food and fat content (D50).

XII. The parties' final requests, where relevant to the present decision, were as follows.

- The patent proprietor requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or, alternatively, one

of auxiliary requests 1 to 10, all filed with its letter dated 26 August 2022.

- The opponents requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. Main request - amendments (Article 123(2) EPC)

1.1 Claim 1 of the main request is directed to a tablet comprising 50 mg bictegravir or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

1.2 The standard of disclosure to be applied for the assessment of added subject-matter is the gold standard, i.e. "*what a skilled person would derive directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, from the whole of these documents [the application documents] as filed*" (G 1/16 Reasons 17 to 20).

1.3 According to the patent proprietor, the primary basis for claim 1 of the main request in the application as filed is claim 7. This claim discloses a tablet as in claim 1 of the main request with the additional limitation that the tablet is coated. Therefore, the question that arises in relation to added subject-

matter is whether claim 7 as filed may be generalised to an uncoated tablet.

1.3.1 In this context, the patent proprietor referred to paragraph [0071] as filed, which teaches that the tablets according to the invention can be coated or uncoated. The paragraph reads:

"*In certain embodiments, tablets provided herein are uncoated. In certain other embodiments, tablets provided herein are coated (in which case they include a coating). Although uncoated tablets may be used, it is more usual in the clinical setting to provide a coated tablet, in which case a conventional non-enteric coating may be used.*"

The opponents argued that paragraph [0071] was not generally applicable to the whole content of the application as filed because it was in a section relating to the disclosure of specific embodiments.

The board disagrees. Paragraph [0071] is in a part of the description starting in paragraph [0053] which discloses different aspects of the tablets according to the invention, such as their total weight, excipients, physical properties, etc. However, there is no doubt that the teaching in paragraph [0071] that the tablets of the invention can be coated or uncoated is generally applicable. Only later in the paragraph are particular aspects of coating discussed.

1.3.2 The patent proprietor also drew attention to several embodiments in the application as filed which disclose tablets containing the active ingredients in claim 7 as filed without specifying that the tablets are coated or

uncoated. This was in particular the case for claims 6, 9 and 11.

Claim 6 as filed, which is dependent on claim 1 as filed, discloses a tablet as in claim 7 as filed with the difference that it does not specify the amounts of active ingredients nor whether the tablet is coated or uncoated.

Claim 9 as filed differs from claim 7 as filed in that it contains the additional limitations that the 50 mg of bictegravir or a pharmaceutically acceptable salt thereof and the 25 mg of tenofovir alafenamide or a pharmaceutically acceptable salt thereof are segregated and that the tablet has a total weight of less than about 1 g. However, claim 9 as filed is broader than claim 7 in that it does not specify whether the tablet is coated or uncoated.

With regard to claim 11 as filed, it does not disclose the absolute amounts of active ingredients in claim 7 as filed but discloses narrow ranges of weight percentage which are compatible with the amounts in claim 7 as filed, namely 6.5 to 11 wt.% bictegravir or a pharmaceutically acceptable salt thereof, 3.0 to 4.5 wt.% tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25 to 30 wt.% emtricitabine or a pharmaceutically acceptable salt thereof. Claim 11 does not specify whether the tablet is coated or uncoated, either.

1.3.3 The patent proprietor also mentioned claim 8 as filed. This claim discloses a tablet as in claim 7 as filed in which bictegravir is limited to its sodium salt and tenofovir alafenamide is limited to its hemifumarate

salt. Like claims 6, 9 and 11, claim 8 as filed does not specify whether the tablet is coated or uncoated.

1.3.4 Similar disclosures to those in the claims can also be found in passages of the description of the application as filed, such as paragraphs [0010], [0016] and [0053]. For instance, paragraph [0053] discloses in the last full sentence on page 10 a solid oral dosage form containing the active ingredients and amounts of claim 7 as filed with the limitation that the oral dosage form comprises between 425 and 450 mg of excipients. Paragraph [0053] does not specify whether the oral dosage form is coated or uncoated. Although the paragraphs above generally refer to oral solid dosage forms, the only oral solid dosage form disclosed in the application as filed is a tablet.

1.4 Given the plurality of embodiments in the application as filed that are closely related to the tablet of claim 7 as filed (broader, narrower and overlapping), that those embodiments do not require the tablet to be coated, and that the application generally teaches that tablet coating is optional, the board holds that the skilled person would directly and unambiguously derive a tablet as defined in claim 1 as granted from the application as filed.

Therefore, claim 1 of the main request meets the requirements of Article 123(2) EPC.

2. Main request - novelty (Article 54(3) EPC)

2.1 The opponents raised a novelty objection based on document D1. It was undisputed that D1 was prior art under Article 54(3) EPC.

2.2 The opponents primarily relied on paragraph [0096] of D1, which reads as follows (emphasis added by the board):

"*In certain embodiments, a compound disclosed herein is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 5-10; 5-15; 5-20; 5-25; 25-30; 20-30; 15-30; or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine.* ***In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine****. A compound as disclosed herein (e.g.,* ***a compound of formula (II)****) may be combined with the agents provided herein in any dosage amount of the compound (e.g.,* ***from 50 mg to 500 mg of compound****) the same as if each combination of dosages were specifically and individually listed.*"

The appellants focused on the embodiment emphasised by the board, namely the combination of 50 to 500 mg sodium bictegravir (compound of formula II, see paragraph [0008] of D1), 25 mg tenofovir alafenamide or its fumarate or hemifumarate salt, and 200 mg emtricitabine. According to the opponents, paragraph [0096] relates to a fixed-dose tablet because, in their view, this is the preferred and only claimed form of

the compositions in D1. This would be derivable from paragraphs [0065] and [0081] and claim 21.

2.3 The board does not agree with the opponents' interpretation of D1, especially not with the opinion that the combinations disclosed in paragraph [0096] are fixed-dose tablets.

2.3.1 D1 is mainly directed to sodium bictegravir, its crystalline forms and its use for treating or preventing an HIV infection (paragraphs [0002] and [0008] to [0014]). The combination of sodium bictegravir with other anti-HIV active ingredients is disclosed in paragraphs [0069] to [0101] and claims 13 to 21.

2.3.2 Paragraph [0065] does not relate to combination therapy but merely to formulations containing sodium bictegravir. It discloses a plurality of possible formulations, including tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. The paragraph states that, in a specific embodiment, the pharmaceutical composition is a tablet. Later on, it also states that the composition will be administered in one or more dosage units and that, for example, a tablet may be a single dosage unit and a container of a compound of the invention in aerosol form may hold a plurality of dosage units.

As paragraph [0065] is not in the section relating to combination therapy, it can hardly be combined with paragraph [0096] or be considered to relate to fixed-dose tablets. Furthermore, the paragraph discloses different types of formulations and does not clearly teach that tablets are the most preferred ones. This is

confirmed by subsequent paragraphs [0066] and [0067] which disclose solutions and suspensions for injection and tablets, pills and capsules for oral administration.

2.3.3 Paragraph [0081] teaches that, in certain embodiments, sodium bictegravir is formulated as a tablet that can further contain one or more other compounds useful for treating HIV. It also states that, in certain embodiments, such tablets are suitable for once daily dosing.

The board agrees with the opponents that paragraph [0081] discloses a fixed-dose tablet containing sodium bictegravir in combination with other compounds useful for treating HIV. However, it cannot be derived from D1 that this embodiment is particularly preferred. As noted by the patent proprietor, paragraphs [0098], [0100] and [0101] disclose that when sodium bictegravir is combined with one or more additional therapeutic agents, the compounds can be administered simultaneously or sequentially. This means that when D1 discloses a combination of sodium bictegravir with other active ingredients, such as in paragraph [0096], the active compounds are not necessarily formulated together in a fixed-dose tablet. They can be provided in more than one formulation to be administered simultaneously or sequentially.

2.3.4 This situation does not change when the examples and the claims are considered.

The examples of D1 focus on the characterisation of sodium bictegravir crystalline forms and the study of their stability and bioavailability. They do not illustrate sodium bictegravir formulations, even less

formulations containing additional anti-HIV active ingredients.

Claims 20 and 21, which refer back to claims 12 to 18, disclose a tablet as a unit dosage form of sodium bictegravir which optionally contains one to three additional therapeutic agents such as tenofovir alafenamide hemifumarate and emtricitabine. The tablet in accordance with claims 20 and 21 can contain sodium bictegravir alone (when dependent on claim 12) or in combination with one to three additional therapeutic agents (when dependent on claims 13 to 18).

Therefore, even if a tablet is the only formulation claimed in D1, this does not necessarily imply that the combination of sodium bictegravir, tenofovir alafenamide and emtricitabin in paragraph [0096] is a fixed-dose tablet containing the three active ingredients.

2.4 Consequently, it cannot be directly and unambiguously derived from a general reading of D1 that the combinations disclosed in paragraph [0096] are fixed-dose tablets. For this reason alone, the subject-matter of the main request is novel over D1.

3. Main request - inventive step (Article 56 EPC)

3.1 The patent relates to the treatment of an HIV-1 infection. At the filing date, it was common general knowledge that the recommended therapy for antiretroviral naive patients was a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with a third agent belonging to one of the following classes: ritonavir-boosted protease inhibitors (PI/r), non-nucleoside reverse transcriptase inhibitors

(NNRTIs) or integrase inhibitors (INIs). The preferred NRTI backbone was the combination of tenofovir and emtricitabine and the preferred third agent was one of atazanavir/r, darunavir/r, dolutegravir, elvitegravir/c, raltegravir and rilpivirine (D7, page 13, Table 5.1).

3.2 The patent aims to provide a fixed-dose combination of active compounds suitable for treating HIV-1 infection by oral administration (paragraphs [0001] and [0003]). The combination of the invention contains bictegravir, tenofovir alafenamide and emtricitabine (paragraph [0056]).

Bictegravir belongs to the class of INIs (paragraph [0035]). In Examples 3 and 9, the patent discloses the results of bioavailability studies in healthy subjects under fed and fasted conditions. The studies include the administration of a tablet containing 100 mg bictegravir as the sole active ingredient (paragraph [0324]) and tablets containing a combination of 75 or 50 mg bictegravir, 25 mg tenofovir alafenamide and 200 mg emtricitabine (paragraphs [0327] and [0354]). It was found that a tablet according to claim 1 (Formulation F7) provided suitable exposure to each of the three active ingredients and that this was not strongly affected by the food intake. Therefore, the tablet could be administered without regard to food (paragraphs [0355] to [0356]).

3.3 The opponents considered that the closest prior art was D5, in particular the preferred embodiment disclosed in the passage bridging pages 19 and 20. The embodiment reads:

"*In an alternatively preferred embodiment the pharmaceutical composition of the present invention comprises about 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir (c), in particular tenofovir alafenamide*".

The patent proprietor contested that this embodiment was a suitable starting point because it falls outside the core of the invention of D5, which requires the weight ratio of dolutegravir to emtricitabine to be 1:1 to 1:3 (page 3, lines 18 to 20 and claim 1).

D5 generally relates to compositions comprising a combination of dolutegravir, emtricitabine and tenofovir having specific weight ratios of dolutegravir to emtricitabine (page 3, lines 8 to 11 and 15 and 16). The patent proprietor is correct that compositions having a weight ratio of dolutegravir to emtricitabine of 1:1 to 1:3 are at the core of the teaching of D5 (page 3, lines 18 to 20 and claim 1). However, D5 does not exclude other weight ratios, as is apparent from the passages on page 16, lines 8 to 13, page 19, lines 3 to 8, page 19, line 23 to page 20, line 8, and from Table 1 on page 25 and Table 2 on page 26. In addition, as argued by the opponents, the skilled person having in mind common general knowledge (D7, Table 5.1) and the HIV-1 inhibition results in Tables 1 and 2 of D5 would consider that a fixed-dose combination of dolutegravir, tenofovir alafenamide and emtricitabine as defined in the passage bridging pages 19 and 20 of D5 was suitable for the treatment of HIV infection.

Therefore, the board agrees with the opponents that the embodiment bridging pages 19 and 20 of D5 can be taken as the closest prior art. This selection of the closest prior art does not negatively affect the patent

proprietor (see point 3.8 below) and no further discussion of this point is therefore necessary.

3.4 The parties did not dispute that the integrase inhibitor in claim 1 was a difference over the closest prior art (bictegravir instead of dolutegravir). They disagreed on whether the formulation of the active ingredient combination as a tablet was a second difference. However, it was common ground that this possible second difference was not critical. In view of the outcome of the assessment of inventive step below (point 3.8), this issue can be left open.

3.5 With regard to the technical effect produced by replacing dolutegravir with bictegravir, the opponents did not dispute that the fixed-dose combination tablet in claim 1 was safe and effective for treating an HIV-1 infection. This was derivable from common general knowledge about the anti-HIV activity of the backbone combination tenofovir alafenamide and emtricitabine (D7, page 13, Table 5.1) and the pharmacokinetic studies on Tablet F7 in Example 9 of the patent. Tablet F7 is a tablet in accordance with claim 1 (see Example 6) which, in Example 9, was shown to provide suitable exposure to each of the active ingredients (paragraph [0352]).

The suitability of the tablet in claim 1 for treating HIV-1 infection was confirmed in post-published document D36, the assessment report of the European Medicines Agency on Biktarvy. The latter is a tablet in accordance with claim 1 indicated for the treatment of HIV-1 (page 2; page 103, point 4, section "Outcome").

As an additional technical effect, the patent showed in subsequent pharmacokinetic studies in Example 9, that

the previously observed exposure of the active ingredients in Tablet F7 was not substantially affected by food. This meant that the fixed-dose combination tablet of claim 1 could be taken without regard to food (paragraphs [0355] and [0356]). The opponents did not contest this technical effect, either.

The technical effects disputed by the parties were a reduction in the food effect compared to a fixed-dose combination containing 75 mg bictegravir, an improvement in the resistance profile and an improvement in forgiveness for missed doses. In view of the outcome of the assessment of inventive step below, a discussion of these disputed effects is not necessary in the present decision.

3.6 Therefore, the board considers that the objective technical problem is to provide a composition suitable for treating HIV infection which can be taken without regard to food.

3.7 On the issue of obviousness, the opponents relied on the common general knowledge on HIV treatment disclosed in D7 and the teaching in documents D3 and D18.

3.7.1 D7 is the British HIV Association guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy. As set out in point 3.1 above, D7 teaches in Table 5.1 (page 13) that the recommended therapy for antiretroviral naive patients is a backbone of two NRTIs combined with a third agent. The preferred NRTI backbone is a combination of tenofovir and emtricitabine, and the preferred third agent is atazanavir/r, danuravir/r, dolutegravir, elvitegravir/c, raltegravir or rilpivirine.

D3 is a patent application which discloses a family of HIV integrase inhibitors (INIs) and their use to reduce HIV replication (page 3, lines 8 to 16). Compound 42 on page 99 of D3 is bictegravir. In Example 104, 103 compounds of the family were tested for their antiviral activity and Compound 42 was among the most potent ones (Table 1, page 214). In Example 107, the bioavailability of the 11 most promising candidates, including Compound 42, was tested in beagle dogs (Table 4, page 224).

D18 is a document from the World Health Organisation proposing International Nonproprietary Names (INNs). On page 205, it proposes the INN bictegravir for the compound disclosed in claim 1 of the main request. Opponent 1 submitted that the proposal of an INN meant that bictegravir was at an advanced stage of clinical development.

3.7.2 According to the opponents, the skilled person wanting to solve the objective technical problem would keep the NRTI backbone of tenofovir and emtricitabine in D5 and would then replace the third agent dolutegravir with another third agent. As dolutegravir was an INI, the immediate option was to take another INI, in particular bictegravir which was known to be a potent INI (D3) at an advanced stage of clinical development (D18).

3.7.3 In the board's view, the opponents' approach is based on hindsight.

First, it is unlikely that the skilled person starting from D5 would straightforwardly replace dolutegravir with another INI and keep the dose of 50 mg. This is even more the case considering that the core of the invention in D5 is a combination of dolutegravir,

emtricitabine and tenofovir having a weight ratio of dolutegravir to emtricitabine of 1:1 to 1:3 (see point 3.3. above) rather than 1:4, as required by claim 1.

Second, D7 shows in Table 5.1 that it was common general knowledge that alternatives to dolutegravir as the third agent in combination with the backbone tenofovir/emtricitabine were well-established therapeutic agents, namely atazanavir/r, darunavir/r, elvitegravir/c, raltegravir and rilpivirine. At the filing date, bictegravir was not an established therapy against HIV. At most, it was a promising INI at a certain stage of clinical development. Therefore, the board has doubts as to whether the skilled person would expect the replacement proposed by the opponents to be successful. If bictegravir was to be used as the combination partner of tenofovir and emtricitabine, first its clinical development had to be completed to confirm the safe and effective dose for treating HIV infection as a standard therapy. Then, they would need to study whether bictegravir could be combined with tenofovir and emtricitabine in a fixed-dose formulation. This two-step procedure alone goes beyond routine testing. But on top of this, there is no suggestion in the prior art that the particular choice of bictegravir at a 50 mg dose is suitable for preparing a fixed-dose combination with 25 mg tenofovir and 200 mg emtricitabine that can be administered without regard to food.

For the sake of completeness, the board notes that opponent 3 had also argued that it was obvious to replace 50 mg dolutegravir with 50 mg bictegravir because it was known from D50 (last sentence of the abstract) that a dolutegravir dose of 50 mg could be administered without regard to food and fat content

(statement of grounds of appeal 3, page 9, penultimate paragraph). At the oral proceedings, the board did not admit D50 under Article 12(4) and (6) RPBA. First, D50 added complexity to the proceedings and, at first glance, it was not suited to dealing with the issue of the food effect. As argued by the patent proprietor (reply to the opponents' appeals, point 4.202), even if dolutegravir was known to have a reduced food effect, this did not mean there was any expectation that the same would be true of bictegravir, let alone for a combination of bictegravir with tenofovir and emtricitabine. Second, the food effect of the combination of active ingredients in claim 1 had been extensively discussed during the opposition proceedings. Therefore, D50 could and should have been filed earlier.

3.8 The tablet in claim 1 of the main request is therefore not obvious. The same is true for the use of the tablet defined in claim 8. Consequently, the main request meets the requirements of 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 based on the claims of the main request filed on 26 August 2022, and a description to be adapted thereto if necessary.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated