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Opposition against EP 2 531 027 (11 737 484.3)
"Therapeutic Combination Comprising Dolutegravir, Abacavir And Lamivudine"
Patentee: ViiV Healthcare Company
Opponent: ter Meer Steinmeister & Partner

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In the name and on behalf of

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a notice of opposition against the above-mentioned European patent number EP 2 531 027 B1 in the name of VIIV Healthcare Company is herewith filed. The opposition fee in the amount of EUR 775.00 is paid by online payment.

A. Requests

It is herewith requested to

1. revoke the patent in its entirety according to Art. 101(2) 1st sentence EPC and
2. auxiliary to summon for oral proceedings pursuant to Art. 116 EPC.

The opposition is based on the grounds that the subject-matter is not patentable due to lack of an inventive step pursuant to Art. 100(a) EPC, that the opposed patent does not disclose

the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art pursuant to Art. 100(b) EPC and that the subject-matter extends beyond the content of the application as filed pursuant to Article 100(c) EPC.

B. Facts and Arguments

I. Documents

The opponent will refer to the following documents D1 to D6, which are cited as prior art under Article 54(2) EPC:

D1: Kobayashi et al., "*In Vitro Antiretroviral Properties of S/GSK1349572, a Next-Generation HIV Integrase Inhibitor*", Antimicrob. Agents Chemother., Vol. 55(2), Feb. 2011, p. 813-821, published ahead of print on November 29, 2010

D2: "*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*", Department of Health and Human Services, December 1, 2009, p. 1-161

D3: Somboonwit et al., "*Abacavir and lamivudine combination*", Expert. Opin. Drug Metab. Toxicol., Vol. 5(12), Dec. 2009, p. 1599-606

D4: EP 1 874 117 B1

D5: Young et al., "*A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naïve HIV-1-infected patients: 48-week results of the SHIELD trial*", HIV Clin Trials., Vol. 11(5), Sep.-Oct. 2010, p. 260-269

D6: Prescribing information for "*Epzicom®*" (2004)

II. Subject-Matter of the Opposed Patent

The opposed patent is directed to a combination of the active agents dolutegravir, abacavir and lamivudine, and deals in particular with the therapeutic use of this combination in the treatment of HIV infection (title and paragraphs [0011] and [0012] of the opposed patent).

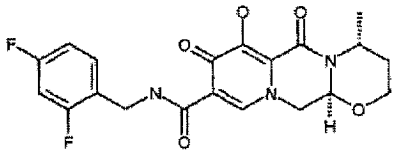
According to the background section of the opposed patent, it was known in the art that "[*A*]*dministration of combinations of therapeutic compounds in the treatment of HIV infection and related conditions can result in potentiated antiviral activity, reduced toxicity, delayed progression to resistance, and increased drug efficacy*" (paragraph [0006] of the opposed patent).

According to the opposed patent, the agents dolutegravir, abacavir and lamivudine as well as their methods of manufacture have been known in the art (paragraphs [0051], [0052] and [0053]). The background section of the opposed patent further acknowledges that dolute-

gravir (also designated as "S/GSK1349572A") has been used in a clinical trial in combination with lopinavir and ritonavir.

The opposed patent includes a total of 9 claims. Independent **claim 1** reads as follows:

A combination comprising a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, abacavir or a pharmaceutically acceptable salt thereof, and lamivudine.

Claims 2 and 3 are directed to preferred embodiments of claim 1.

Claim 4 is directed to the use of the combination of claims 1-3 in medical therapy.

Claim 5 is directed to the use of the combination of claims 1-3 in the treatment of HIV infection.

Claim 6 is directed to a pharmaceutical composition comprising the combination of claims 1-3.

Claims 7 and 8 are directed to preferred embodiments of claim 6.

Claim 9 basically corresponds to claim 5 of the opposed patent, but is formulated in the Swiss type form for medical use claims.

III. The Opposed Patent is not entitled to its Priority

In accordance with Art. 87 EPC a European patent application is only entitled to priority in respect of "*the same invention*" as was disclosed in the previous application, which means that priority is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

The opposed patent claims the priority of application US 298589, having a filing date of January 27, 2010. However, **the priority application does not disclose a combination of dolutegravir**, i.e. the compound of formula (I) or a pharmaceutically acceptable salt there-

of, **abacavir** or a pharmaceutically acceptable salt thereof **and lamivudine**, as required by the independent claims of the opposed patent.

In contrast, the priority document relates to combinations comprising a compound of formula (I), formula (II) or formula (III) with one or more therapeutic agents selected from the group consisting of nucleotide reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, CCR5 antagonists, CXCR4 antagonists, fusion inhibitors, maturation inhibitors, and integrase inhibitors (see page 3, line 16 to page 4, line 7 of the priority document). In particular, the priority document relates to a combination comprising a compound of formula (I) with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir (claim 1 of the priority document). However, there is neither a disclosure nor teaching of the combination of compounds of claim 1 of the opposed patent.

Therefore, the priority application does not disclose the same invention as the opposed patent.

In consequence, the opposed patent is not entitled to its priority. Therefore, **the effective date** for defining the relevant state of the art is the filing date of the PCT application WO 2011/094150 of **January 24, 2011**.

IV. Grounds for Opposition according to Art. 100 EPC

1. The Claims as Granted Extend Beyond the Content of the Application as Filed, Contrary to Art. 123(2), 100(c) EPC

1.1 According to the applicant's submission dated December 06, 2013 during the examination proceedings of the opposed patent, claim 1 as granted is based on claims 1, 2 and 4 and page 9, lines 22 to 26 as originally filed in the PCT application WO 2011/094150 A1. According to claim 2 as filed, the therapeutic agent is abacavir and according to claim 4 the therapeutic agent is lamivudine. The cited paragraph on page 9, lines 22 to 26 discloses that "*one or more therapeutic agents are a pharmaceutically acceptable salt of said therapeutic agents*".

Therefore, the application as filed clearly distinguishes between the therapeutic agent as such, e.g. abacavir and lamivudine, and pharmaceutically acceptable salts thereof. According to claim 2 as filed, which has been included into claim 1, the therapeutic agent is ab-

acavir, whereas the pharmaceutically acceptable salt thereof is not mentioned in claim 2. Hence, claim 2 cannot be used as disclosure for supporting the amendment in claim 1.

The cited section on page 9, lines 22 to 26 only discloses that "*one or more*" therapeutic agents are a pharmaceutically acceptable salt, without specifying, which of the three agents of claim 1 is provided as a pharmaceutically acceptable salt. Hence, a **three-fold selection** would have to be made, i.e. a selection for each of the three therapeutic agents, to select between the salt form and the non-salt form thereof. However, a three-fold selection creates a new embodiment, which is not as such disclosed in the application as filed.

In consequence, the combination of a pharmaceutically acceptable salt of abacavir together with the other features of claim 1 is not originally disclosed. Thus, claim 1 as granted contravenes Article 123(2) EPC.

1.2 In addition, the application as filed does not support the combination of lamivudine and the sodium salt of the compound of formula (I), as in claim 2 of the opposed patent. Lamivudine has been disclosed in original claim 4, which however was dependent on claim 2 only, specifically claiming abacavir, but not dependent on claim 3 as filed, claiming the sodium salt of the compound of formula (I). Hence, also the combination of features of claim 2 as granted contravenes Article 123(2) EPC.

2. Insufficiency of Disclosure, Contrary to Art. 83, 100(b) EPC

2.1 According to established case law, it is necessary under Article 83 EPC that a patent discloses at least one way to carry out the invention. As described in Chapter II.C-4.2 of the "*Case Law of the Boards of Appeal of the EPO*", 7th Edition, 2013:

> "*An invention is in principle sufficiently disclosed* ***if at least one*** *way is clearly indicated enabling the person skilled in the art to carry out the invention. If this is the case, the non-availability of some particular variants of a functionally defined component feature of the invention is immaterial to sufficiency as long as there are suitable variants known to the skilled person through the disclosure or common general knowledge which provide the same effect for the invention (T 292/85, OJ 1989, 275). This has been confirmed by many decisions, for example: T 81/87 (OJ 1990, 250), T 301/87 (OJ 1990, 335), T 212/88 (OJ 1992, 28), T 238/88 (OJ 1992, 709), T 60/89 (OJ 1992, 268), T 182/89 (OJ 1991, 391), T 19/90 (OJ 1990, 476), T 740/90, T 456/91 and T 242/92.*" (emphasis added)

Although there is no requirement under the EPC that an application or a patent must necessarily disclose one or more specific examples, as "*the presence of examples would only be indispensable if the description would otherwise not be sufficient to meet this requirement.*" (II.C-4.3 of the "Case Law" book of the EPO), the skilled person is not enabled by the opposed patent as a whole, i.e. even taking the claims and the general description into account, to rework the claimed subject-matter in all its essential aspects in order to achieve the desired effects.

It is emphasized that according to paragraph [0006] of the opposed patent:

> "*However, not all compounds are suitable for administration in combinations. Factors that influence the feasibility of combinations include the chemical instability of the compounds, size of the dosage unit, potential for antagonistic or merely additive activities of the combined compounds, and difficulties in achieving a suitable formulation.*"

Thus, the opposed patent itself emphasizes that not all compounds can be combined into a combination preparation, for example for joint use, as there are various factors, which influence suitability of compounds to be combined with other compounds for their combined therapeutic use.

In view of the above, **the presence of one or more experimental examples in the opposed patent is indispensable**, in order to demonstrate the feasibility of the active agents to be combined in a combination preparation, and to demonstrate their efficacy in the treatment of HIV infection. However, the opposed patent lacks any data or examples showing that the claimed invention can actually be put into practice.

Hence, although the opposed patent itself acknowledges that there are a variety of factors influencing whether active agents are at all feasible and suitable for being combined in a combination preparation, the opposed patent lacks any data or examples actually demonstrating the suitability of the combination of dolutegravir, abacavir and lamivudine to be combined in a combination preparation and being therapeutically effective, for example in the treatment of HIV infection.

Hence, the opposed patent does not fulfil the requirements of Article 83 EPC for this reason alone.

Should the Opposition Division be of the opinion that the skilled person would, however, know on the basis of his or her general knowledge how to combine the three ac-

tive agents (which as such have been well known in the art as acknowledged in the opposed patent) for the achievement of the desired effects, such as the treatment of HIV infection, **than this should be considered in the assessment of an inventive step.**

2.2 According to established case law, it is further necessary under Article 83 EPC that a patent directed to a (second) medical use shows that the claimed compound(s) or composition is actually suitable to treat the medical indication. Reference is made in that respect to the "*Case law of the Boards of Appeal*" (2013), Chapter II-C, 6.2:

> "*In T 609/02 the board pointed out that where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in G 5/83 (OJ 1985, 64), i.e. in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G 2/88, OJ 1990, 93) and G 6/88, (OJ 1990 114) for non-medical applications). As a consequence,* ***under Art. 83 EPC****, unless this is already known to the skilled person at the priority date,* ***the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application***." (Emphasis added)

However, in contrast to the criteria set out in T 609/02 **the opposed patent does not disclose the suitability of the combination of dolutegravir, abacavir and lamivudine for any therapeutic application** as claimed in claim 4 of the opposed patent, and in particular **does not disclose the suitability of the claimed combination of compounds in the treatment of HIV infection** as claimed in claim 5 of the opposed patent.

It is emphasized that the opposed patent acknowledges in paragraphs [0008], [0009] and [0051] to [0053] that the active agents dolutegravir, abacavir and lamivudine as such have been well known in the art before the effective date of the opposed patent. Further, their use as active agents in relation with the treatment of HIV infection has also been well known in the art.

Reference is made in that respect to the "*Case law of the Boards of Appeal*" (2013), Chapter II-C, 6.1.2:

> "*When examining sufficiency of disclosure, the boards have to be satisfied, firstly, that the patent specification places the skilled person in possession of at least one way of putting the claimed invention into practice, and secondly, that* ***the skilled person can put the invention into practice over the whole scope of the claim*** *(see*

e.g. T 792/00, T 811/01, T 1241/03, T 364/06). ***The scope of the patent should be justified by the technical contribution to the art*** *(T 612/92).*"

The opposed patent now claims in claim 4 that the combination of dolutegravir, abacavir and lamivudine would be suitable for **any** kind of medical therapy, including even diseases and disorders not related to HIV infection or even other viral infections. The opposed patent, however, lacks any kind of evidence that such a combination would at all be suitable for medical therapy, i.e. that such a combination would be therapeutically effective at all.

The opposed patent contravenes the requirements of Article 83 EPC for this reason additionally.

3. Lack of an Inventive Step, Contrary to Art. 56, 100(a) EPC

3.1 Lack of an Inventive Step in view of D1 as Closest Prior Art

3.1.1 Closest Prior Art and Technical Problem

D1 may be considered as the **closest prior art** document.

D1 deals with the antiviral properties of S/GSK1349572 (i.e. dolutegravir) in particular in the treatment of HIV infection (title and abstract of D1). The identity of dolutegravir and the compound S/GSK1349572 is evident from the chemical structures shown in claim 1 of the opposed patent as well as page 814 of D1. D1 discloses that dolutegravir "*is a next-generation HIV integrase (IN) inhibitor designed to deliver potent antiviral activity with a low-milligram once-daily dose requiring no pharmacokinetic (PK) booster*" (lines 1-2, abstract of D1). Further, D1 describes that dolutegravir has shown potent antiretroviral activity and short-term tolerability in phase 2a studies, which led to the initiation of phase 2b and phase 3 clinical studies (first paragraph on page 814).

In particular, according to D1 dolutegravir has been developed as a next-generation HIV integrase inhibitor (INI), because clinical resistance to the first generation HIV integrase inhibitors raltegravir and elvitegravir has been observed, and a high degree of cross-resistance between these two agents has been demonstrated. Further, long-term safety and/or drug interaction concerns have been raised against these two first-generation HIV integrase inhibitors (middle of the right-hand column, page 813 of D1).

It has been found in D1 that **dolutegravir inhibited both the HIV integration reaction** strand transfer step **and HIV replication** in cells with similar potencies (first full para-

graph, left column, page 819). Further, the compound showed potency against integrase-resistant single and most double or more mutants (right column, page 819).

D1 further emphasized that "[S]*ince INIs will be used in combination regimens, it is important to evaluate the potential synergy and antagonism.* Hence, dolutegravir was tested in combination assays with representatives of all approved classes of HIV therapeutics, including abacavir. It could be shown that **dolutegravir was synergistic with abacavir** (Table 4 and paragraph bridging pages 817 and 818 of D1).

Thus, the **difference** between the subject-matter of claim 1 of the opposed patent and D1 is the combination of dolutegravir and abacavir with lamivudine as third component of the combination of claim 1.

As the opposed patent lacks any data showing the therapeutic effectivity of the claimed combination or any other technical effect, the **technical problem** to be solved by the opposed patent is the provision of an **alternative** combination of active agents.

3.1.2 The Solution to the Technical Problem has been obvious from the Skilled Person's Common Knowledge.

It clearly belonged to the skilled person's general knowledge on or before the filing date of the opposed patent that treatment of HIV infection is most efficient when a combination of two or three different active agents is administered. Such combinations not only have potentiated antiviral activity, but also increase the patient's compliance and have reduced toxicity and delayed progression of virus resistance. This has been acknowledged in paragraph [0006] of the opposed patent.

The skilled person in the technical field of HIV infection treatment and HIV therapy will also clearly have known the "*Guidelines for the use of antiretroviral agents in HIV-infected patients*", submitted herewith as **D2** and representing the skilled person's common knowledge, as well as the marketed and FDA approved drug combinations described therein. As mentioned in D2, HIV infection treatment usually employs a combination of antiretroviral drugs, which typically combine two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (First paragraph, page 37 of D2):

> "*There are more than 20 approved antiretroviral drugs in 6 mechanistic classes with which to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs),*

CCR5 antagonists, and integrase strand transfer inhibitors (INSTI). The most extensively studied combination regimens for treatment-naïve patients that provide durable viral suppression generally consist of ***two NRTIs plus either one NNRTI or a PI (with or without ritonavir boosting). In July 2009, a regimen consisting of raltegravir was approved for treatment-naïve patients, making the combination of an INSTI + 2 NRTIs an additional option****.*" (emphasis added)

The above is further reflected in the last paragraph on page 38 of D2:

"*Recommended regimens use combinations of* ***two NRTIs with*** *an NNRTI, PI (preferably boosted with ritonavir), or* ***an INSTI****, namely raltegravir. In many clinical trials, NNRTI-, PI-, and INSTI-based regimens result in suppression of HIV RNA levels and CD4 T-cell increases in a large majority of patients [1-6].*"

Starting from D1 as closest prior art, which has established dolutegravir as the next-generation HIV integrase and knowing that recommended combination therapies typically employ two different reverse transcriptase (RT) inhibitors in order to achieve the effects mentioned in paragraph [0006] of the opposed patent, **the skilled person would thus clearly have tried to combine dolutegravir with two different reverse transcriptase (RT) inhibitors**.

One of such combinations of RT inhibitors, which has been well established and available as antiretroviral combination, is the combination of abacavir and lamivudine (page 47 of D2 under "*Alternative Dual NRTIs*"). As further listed in Appendix B, Table 1 on pages 152 and 153 of D2 under the respective generic trade names, the combination of abacavir and lamivudine has been marketed in the US as Epzicom® as a one tablet once daily regimen.

The efficacy of the combination of abacavir and lamivudine in the treatment of HIV infection is further described in **D3**. As noted in lines 3-4 under "*Overview of the market*" on page 1599: "*This combination has shown efficacy, few drug interactions and a favourable long-term toxicity profile.*" It is further mentioned under "*Introduction of the compound*" on page 1600 of D3 that: "*The combination of lamivudine and abacavir was approved by the FDA on August 2, 2004*".

In addition, D6, which is the prescribing information for the marketed product Epzicom®, already describes on page 7 under "Antiviral Activity":

> "***Abacavir/lamivudine had additive to synergistic activity in vitro in combination with the nucleoside reverse transcriptase inhibitors*** *(NRTIs: emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine), the non-nucleoside reverse transcriptase inhibitors (NNRTIs: delavirdine, efavirenz, nevirapine), the protease inhibitors (PIs: amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), or the fusion inhibitor, enfuvirtide.*" (emphasis added)

In consequence, the skilled person knowing from D1 that **dolutegravir and abacavir display synergy** in the treatment of HIV infection, and further knowing from D2 and/or D3 that abacavir and lamivudine is a well established and marketed combination of RT inhibitors, would have combined the three active agents in order to potentiate antiviral activity, to increase the patient's compliance, to reduce toxicity and to delay progression of virus resistance.

As it has further been known from D6 that **abacavir and lamivudine display synergy** when combined with many other anti-HIV agents belonging to different antiviral classes, it would have been a direct consequence for the skilled person to combine the three agents dolutegravir, abacavir and lamivudine in order to potentiate their antiviral efficacy.

The skilled person starting from D1 as closest prior art would thus have solved the technical problem in an obvious manner by his or her general knowledge as represented by D2.

Therefore, the provision of the combination of dolutegravir, abacavir and lamivudine as in claim 1 of the opposed patent, as well as use of such combination in medical therapy, such as in the treatment of HIV infection, as claimed in claims 4, 5 and 9 of the opposed patent, does not involve an inventive step.

3.2 Lack of an Inventive Step in view of D4 as Closest Prior Art

3.2.1 Closest Prior Art and Technical Problem

Should the Opposition Division come to the conclusion that, in contrast to the submission under item III. above, the opposed patent would be entitled to its priority, **D4** would represent the closest prior art document.

D4 deals with dolutegravir and its use as anti HIV-agent (claim 1 and paragraph [0001] of D4). The identity of the compound referred to in claim 1 of D4 and dolutegravir can be seen from the chemical name of claim 1 as well as from the cross-reference for the manu-

facture of the compound of formula (I) in paragraph [0051] of the opposed patent to the PCT-application underlying D4.

D4 discloses that dolutegravir "*has the remarkable inhibitory action on integrase of a virus*" and that it "*is useful as an integrase inhibiting agent for retrovirus [...] and is useful as an anti-HIV drug etc.*" (paragraph [0014] of D4).

D4 further discloses that:

> "*In addition, **the present compound may be used in joint use therapy by combining an anti-HIV drug having the different action mechanism such as a reverse transcriptase inhibiter** and/or a protease inhibiting agent. Particularly, currently, an integrase inhibiter is not marketed, and it is useful to use in **joint use therapy by combining the present compound with a reverse transcriptase inhibiter** and/or a protease inhibiter.*" (paragraphs [0015] and [0016] of D4, emphasis added).

Therefore, D4 not only suggests use of dolutegravir in a medical mixture for anti-HIV, but also suggests its use as a joint use agent for increasing the anti-HIV activity of other anti-HIV drugs, such as in a cocktail therapy.

As D4 thus already suggests the joint use of dolutegravir with a reverse transcriptase inhibitor, the only **difference** between the subject-matter claimed in the opposed patent and D4 is to use abacavir and lamivudine as the reverse transcriptase inhibitors.

As the opposed patent lacks any data showing the therapeutic effectivity of the claimed combination or any other surprising technical effect, the **technical problem** to be solved by the opposed patent is the provision of an **alternative** combination of dolutegravir with reverse transcriptase inhibitors.

3.2.2 The Solution to the Technical Problem has been obvious from the Skilled Person's Common Knowledge.

In view of the D4 as closest prior art, the skilled person would have been sufficiently motivated to combine dolutegravir with RT inhibitors in a combination therapy, as D4 already suggests to use dolutegravir in joint therapy together with RT inhibitors.

D2 and/or **D3** already disclose that the combination of abacavir and lamivudine is an established and marketed combination of such RT inhibitors. In consequence, the skilled person would have combined dolutegravir with abacavir / lamivudine in an obvious manner and

with great expectation of success. Consequently, the skilled person would have used such a combination in the treatment of HIV infection.

Therefore, the provision of the combination of dolutegravir, abacavir and lamivudine as in claim 1 of the opposed patent, as well as use of such combination in medical therapy, such as in the treatment of HIV infection, as claimed in claims 4, 5 and 9 of the opposed patent, does not involve an inventive step. Hence, the opposed patent lacks an inventive step when starting from D4 as closest prior art.

3.3 Obviousness of the Opposed Patent in view of D1/D4 and D5

Starting from **D1** as closest prior art, the skilled person would have found further support to actually combine dolutegravir with abacavir and lamivudine from **D5**.

D5 summarizes the results of a pilot study assessing the efficacy of raltegravir when used together with abacavir and lamivudine in HIV-infected patients. It could be found in D5 that abcavir/lamivudine plus raltegravir has been effective in the treatment of HIV-infection and generally well tolerated over 48 weeks (see "Conclusions" in the abstract of D5).

In consequence, the skilled person would have known from D5 that the integrase inhibitor raltegravir is effective when used in combination with the RT inhibitors abacavir / lamivudine.

Raltegravir was the first integrase inhibitor that received FDA drug approval for the treatment of HIV infection in 2007 (middle of the right-hand column, page 813 of D1). However, as reported in the introductory section of D1, clinical resistance to raltegravir had been reported. Further, there have been long-term safety concerns and/or drug-drug interaction concerns. These concerns have been addressed in the development of dolutegravir as next-generation integrase inhibitor (last sentence of the first full paragraph, of the right-hand column, page 813 of D1).

In view of the clinical resistance and safety concerns reported in D1, the skilled person would have been sufficiently motivated to replace the integrase inhibitor raltegravir in the combination raltegravir / abacavir / lamivudine of D5 by a next-generation integrase inhibitor, such as dolutegravir, in order to overcome the problems addressed in D1 with respect to raltegravir.

The skilled person starting from D1 as closest prior art would thus have arrived in an obvious manner at the combination of active agents claimed in claim 1 of the opposed patent by taking D5 into account.

The same conclusions as above must also be drawn when starting from **D4** as alternative closest prior art. D4 already suggests using dolutegravir together with RT inhibitors, such as abacavir and lamivudine. As abacavir and lamivudine have already been found effective in **D5** in the treatment of HIV-infection when used in combination with an integrase inhibitor, the skilled person would have replaced raltegravir in an obvious manner by dolutegravir as an alternative integrase inhibitor.

In consequence, claim 1 of the opposed patent does not involve an inventive step in view of D1 or D4 in combination with D5. Claims 4, 5 and 9 lack an inventive step for the same reasons as discussed above for claim 1. In particular, all the above-mentioned prior art documents deal with the treatment of HIV infection. Hence, the feature of use of the combination of claim 1 in medical therapy, such as in the treatment of HIV infection, cannot establish an inventive step, but has likewise been obvious from the cited documents.

3.4 Lack of an Inventive Step of the Dependent Claims

Claim 2 is directed to the sodium salt of the compound of formula (I) of claim 1, i.e. of dolutagravir. However, the subject-matter of claim 2 is already anticipated by claim 2 of D4, which likewise claims the sodium salt of dolutegravir, i.e. the compound of claim 1 of D4. Besides, no surprising and unexpected technical effect is shown in the opposed patent resulting from (use of) the sodium salt of dolutegravir. Hence, its provision would be obvious for the skilled person for this reason additionally.

Claim 3 is directed to the hemisulfate salt of abacavir. However, abacavir is conventionally used in the art in form of the semisulfate salt, as can be seen from the product description of Epzicom® in which abacavir is used as the sulfate salt (page 1600 of D3 under "Introduction of the compound" and D6, pages 5-6 under "Abacavir Sulfate"). The indication as (2:1) salt and the chemical formula shown on top of page 6 of D6 also clarify that abacavir "sulfate" means its "hemisulfate". Besides, no surprising and unexpected technical effect is shown in the opposed patent resulting from (use of) abacavir as the hemisulfate salt. Hence, its provision would be obvious for the skilled person for this reason additionally.

Claim 6 is directed to a pharmaceutical composition comprising the combination of claims 1-3 together with a pharmaceutically acceptable carrier. However, D4 already suggest

providing dolutegravir in the form of a pharmaceutical composition comprising a pharmaceutically acceptable carrier (paragraph [0018] of D4). Further, Epzicom® is also marketed as tablets for oral administration containing as the active ingredients 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. (see D6, page 5 under "*Description*" as well as D3, "*Introduction to the compound*", page 1600). Hence, claim 6 cannot add anything inventive, as the provision of the combination of dolutegravir, abacavir and lamivudine as a pharmaceutical composition including a pharmaceutically acceptable carrier has been obvious in the art.

According to **claim 7** the combination of claims 1-3 is administered simultaneously, and according to **claim 8** sequentially. However, in the absence of any surprising or unexpected technical effect, such features cannot add anything inventive, because the skilled person would chose the most beneficial administration scheme, i.e. either simultaneous or sequential administration of active agents, which provides the optimal combination of patient's compliance and therapeutic effect. Thus, claims 7 and 8 likewise lack an inventive step.

IV. Conclusions

Considering the above arguments it becomes evident that the opposed patent does not fulfil the patentability requirements according to the European Patent Convention.

In particular, the subject-matter of the opposed patent is not patentable as it is rendered obvious by the prior art and thus does not involve an inventive step. Further, it extends beyond the content of the application as filed and is not disclosed in a manner sufficient and complete for it to be carried out by a person skilled in the art.

Therefore, the above-mentioned request to revoke the patent in its entirety based on the grounds for opposition under Art. 100(a) to (c) EPC is reasonable and justified.

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Enclosures:
Documents D1 to D6