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Opponent/Representation of:	LEK Pharmaceuticals d.d.
HS 88-OP31286EP00	

[February 5, 2016]

Opposition ./. EP 2 531 027 B1 (VIIV Healthcare Company)

Facts and Arguments

I.
Documents

The following documents are cited and will be referred to in the present opposition:

D1: Prada and Markowitz, Expert Opin. Investig. Drugs 19(9), 1087-1098 (2010)
D2: ClinicalTrials.gov, The Archive 4 September 2009: "A Dose Ranging Trial of GSK1349572 and 2NRTI in HIV-1 Infected, Therapy Naive Subjects (ING112276) (http://web.archive.org/web/20090904062433/http://clinicaltrials.gov/ct2/show/NCT00951015)
D3: Arribas et al., Abstract XVIII International Aids Conference, 18-23 July 2010, Vienna, Austria (http://pag.aids2010.org/Abstracts.aspx?AID=17600)
D4: Rockstroh et al., Journal of the International AIDS Society 13(Suppl 4), O50 (2010)
D5: Young et al. EACS 12th AIDS Conference, November 11-14, 2009
D6: WO2006/116764A published 2 November 2006 & JP4295353B2 (D6A) published 17 April 2009 and partial English translation
D7: Min et al., Antimicrobial Agents and Chemotherapy, Jan 2010, 254-258; published ahead of print 2 November 2009
D8: Guidelines for the Use of Anti-Retroviral Agents in HIV-1-Infected Adults and Adolescents, December 01, 2009, pp. 1-161
D9: Tricot et al., American Journal of Transplantation 9, 1946-1952 (2009)
D10: Young et al., HIV Clin. Trials 11(5), 260-269 (2010)
D11: Johns et al., 17th CROI, Conference on Retroviruses and Opportunistic Infections, San Francisco CA, February 16-19, 2010: "The Discovery of S/GSK1349572: A Once Daily Next-Generation Integrase Inhibitor with a Superior Resistance Profile (http://www.natap.org/2010/CROI/croi_63.htm)
D12: Drug Data Report 32(9), 893-895 (2010)
D13: Underwood et al., IAS 2009-5th Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2009, Cape Town, South Africa

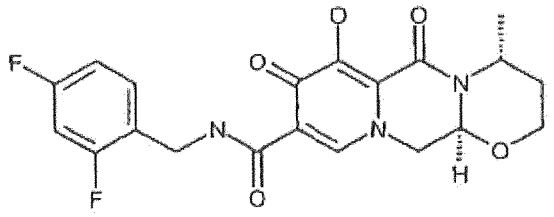
All documents **D1-D13** constitute prior art pursuant to Art. 54(2) EPC. While this is immediately evident for **D2, D5 to D9 and D13**, this is also true for **D1, D3, D4, D10, D11 and D12** given the failure to validly claim priority of US 61/298589 (**P**) (see point III below).

II.
Subject-matter of the opposed patent

1. The patent relates, according to its title, to a therapeutic combination comprising dolutegravir, abacavir and lamivudine. Dolutegravir is the name for the compound of formula (I), also identified as "S/GSK1349572" (cf. e.g. [0008] of the specification of the opposed patent; as will become apparent by the further discussion below, the identifier is often used without the "S").

Specifically, **claim 1** claims a combination comprising

i) the compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

ii) abacavir or a pharmaceutically acceptable salt thereof, and

iii) lamivudine.

In short, and in its simplest form, the subject-matter of claim 1 thus specifies a triple combination of dolutegravir, abacavir and lamivudine.

Not only the compound of formula (I) (respectively its specification [S/]GSK1349572); also the two further combined active compounds sometimes had been identified in the pertinent art by abbreviated identifiers: "ABC" for abacavir, notably its hemisulfate salt (cf. e.g. **D8**, Table 6 on page 52 in the row "Dual-NRTI pairs; legends of Table 5a on page 39 and Table 5b on page 40; **D10**, p. 260 left col.), and "3TC" for lamivudine (cf. again e.g. **D8**, Table 6 and legends of Table 5a on page 39 and Table 5b on page 40; **D10**, p. 260 left col.)

Claim 2 specifies the pharmaceutically acceptable salt of the compound of formula (I) to be the sodium salt. Further, **claim 3** specifies the pharmaceutically acceptable salt of abacavir to be the hemi-sulfate salt.

Claim 4 specifies the combination for use in medical therapy, while **claim 5** further limits the therapeutic application for use in the treatment of HIV infection.

Claim 6 relates to a pharmaceutical composition, comprising the combination of any of claims 1-3 together with a pharmaceutically acceptable carrier therefor.

Claim 7 and **claim 8** relate to the combination of any of claims 1-3 to be administered either simultaneously, or sequentially.

Claim 9 claims the use of the combination of any of claims 1-3 for the manufacture of a medicament for the treatment of HIV infection.

III.
Art. 123(2)/100(c) EPC

The subject-matter of **claim 2** as granted contains information extending beyond the content of the application as originally filed. As the original application documents, reference will be made to the application as published under WO 2011/094150 (in short WO'150).

Specifically, the sodium salt of the compound of formula (I) was defined in **claim 3** of the original application (WO'150). While a combination of the compound of formula (I), abacavir and lamivudine may be supported by the original claims 1, 2 and 4, it is observed that **original claim 4** only refers back to **claim 2**, but **not claim 3**. Therefore, a combination of the compound of formula (I) in the specific form of its sodium salt, in specific conjunction with abacavir and lamivudine, is not directly and unambiguously derivable from the application as filed. Indeed, a combination of original claims 1, 2, 3 and 4 is not supported by virtue of claim 4 referring to claim 2 only.

The statement at page 9, lines 19-21 of WO'150 cannot serve for a direct and unambiguous disclosure basis either, because at least two list selections would have to be done:
from one list where the sodium salt is selected from the compounds of formulae (I), (II) and (III), and furthermore from the list of the very many combinations with classes and lists of

therapeutic agents which are described in the original specification (see e.g. page 6, line 8 to page 7, line 9). Thus, a novel selection is created according to the "two-lists principle" (cf. Examination Guidelines G-VI, 8 (i)), which is not allowable according to the novelty test under Art. 123(2) EPC.

Similar observations apply in view of original claims 5-8, noting that claim 8 refers back to only claim 6, but not to claim 7.

And again likewise observations apply in view of original claims 9 to 12, claim 12 referring back to only claim 10 but not to claim 11.

It follows that the subject-matter of **claim 2**, and likewise the subject-matter of **claims 4** to **9** for the same reasons insofar as these refer to **claim 2**, violate the provision of Art. 123(2) EPC.

IV.
Effective date of the claimed subject-matter (priority)

1. For a priority claim to be valid, it is required that the skilled person can derive the subject-matter of the claims of the opposed patent **directly and unambiguously** from the previous application as a whole (**G 2/98**).

   This means that the priority application US 61/298589 (**P**) dated January 27, 2010 would have to disclose directly and unambiguously the **specific** combination of
   (i) the compound of formula (I) (or a pharmaceutically acceptable salt thereof),
   (ii) abacavir (or a pharmaceutically acceptable salt thereof), **and**
   (iii) lamivudine.

   As will be shown in detail below, this is not the case.

2. It is first observed that the claims of **P** do not mention whatsoever the compound lamivudine to be combined.

3. In view of the general disclosure and the many possible combinations listed in the specification, it is observed that the specific (triple) combination of the compound of

formula (I), abacavir and lamivudine is not directly and unambiguously derivable from the description of **P** either.

3.1 First to mention, a (triple) combination of just three compounds is nowhere disclosed in the specification of **P**.

3.2 The passage at page 3, line 16 to page 4, line 7 of **P** only refers generally to combinations comprising compounds of formula (I), (II) or (III) and one or more therapeutic agents which shall only generally be selected from therapeutic classes, hence providing no basis for the presently claimed specific subject-matter.

3.3 Moreover, the passage from page 6, line 14 to page 7, line 20 of **P** encompasses a virtually unlimited number of combinations from which an individual combination selection would need to be made. There is a first list of compounds encompassing those of formulae (I), (II) and (III), and there is a further list of substantial length starting from page 6, line 28 and continuing through page 7, line 20. Furthermore, this passage discloses combination therapies comprising the administration of any one of the compounds of the first and "**another**" pharmaceutically active agent of the second list, i.e. the whole passage is directed to dual combinations, but is silent about triple combinations. Accordingly, there is no direct and unambiguous disclosure of a triple combination, let alone a triple combination comprising a compound of formula (I) and abacavir and lamivudine.

3.4 Whereas subsequent disclosure from page 9, line 1 ff. relates to other embodiments of a combination comprising a compound of formula (II) or a compound of formula (III), a passage at page 7, last paragraph (lines 22-28) and correspondingly one at page 8, 4th paragraph refer to a combination and a pharmaceutical composition respectively comprising a compound of formula (I) "**and one or more**" therapeutic agents selected from the group consisting of lamivudine, abacavir, tenofovir, efavirenz, GSK2248761, lersivirine, lopinavir, fosamprenavir, and atazanavir". Also this passage does **not directly and unambiguously**, let alone individually, disclose a triple combination of the compound of formula (I) with just abacavir and lamivudine.

Multiple selections would be required to come to the subject-matter of claim 1 of the opposed patent. Firstly, the general term and reference to "one or more therapeutic agents selected from" does not specifically and individually disclose a triple combination. Secondly, from the group of listed compounds, abacavir would have to

be selected. Thirdly, also lamivudine would have to be selected. And fourthly, it is required that precisely the combination of lamivudine plus abacavir would have to be taken in combination with the compound of formula (I).

3.5 It goes without saying that the there's an extreme number of possibilities of combinations basically considered by the disclosure in the priority document. For instance, looking at the context of page 7, last paragraph and correspondingly one at page 8, 4th paragraph, a very high number of multiple combinations is obtained.
If only double, triple and quadruple combinations were considered, this already includes 9 dual plus 72 triple plus 504 quadruple combinations, which means that a sum of 585 combinations do realistically exist. If the choice to be made among compounds of formulae (I), (II) and (III) was considered in addition, then even 27 dual plus 216 triple plus 1512 quadruple combinations, i.e. a sum of 1755 combinations would realistically exist.

The presently claiming, by way of claim 1 of the opposed patent, of one specific triple combination out of this extremely high number of possible combinations is not commensurate with a required disclosure in individualized form.
Also from this view, the corresponding lack of disclosure of the claimed specific triple combination **in individualized form**, and the need for a selection out of an extremely high number of possibilities provided in P, underlines the finding that the subject-matter of claim 1 does not enjoy the priority of P.

4. In conclusion, a specific (triple) combination of (i) a compound of formula (I) or a pharmaceutical acceptable salt thereof, (ii) abacavir or a pharmaceutically acceptable salt thereof, and (iii) lamivudine is not directly and unambiguously disclosed in the priority document P.

5. It follows that the claimed priority of the whole subject-matter of the opposed patent is not valid in substance, and consequently the effective date of the claimed subject-matter is only the filing date, January 24, 2011.

6. As a consequence also documents **D1, D3, D4, D10, D11 and D12** constitute prior art under Art. 54(2) EPC to be taken into account for the assessment of novelty and inventive step.

V.

Lack of novelty (Art. 54 EPC)

1. Lack of novelty in view of Prada and Markowitz (D1)

Document **D1** is a review article about novel integrase inhibitors for HIV. More specifically, **D1** reviews the data available about newly developed integrase inhibitors (INIs), and in this connection also refers to the clinical tests with the compound S/GSK1349572, whose chemical structure is shown in item C. of Fig. 1 in correspondence with the compound of formula (I):

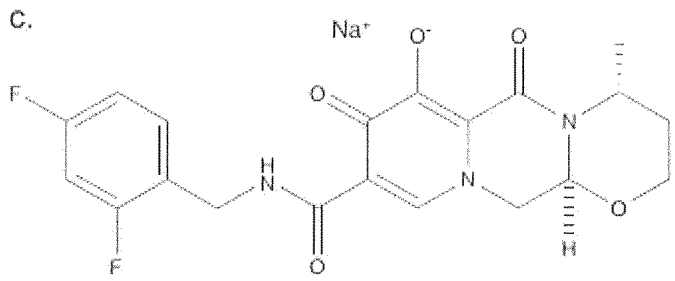


Figure 1. Chemical structures of (A) raltegravir, (B) elvitegravir and (C) S/GSK1349572.

In the key point box at the top of page 1088, this S/GSK1349572 compound is highlighted as a second-generation integrase inhibitor with potent antiviral activity, favorable pharmacokinetics and a potentially higher barrier to the emergence of resistance. According to page 1090, right column, last full paragraph, the details of S/GSK1349572 was first presented at the 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in Cape Town in July 2009, and in connection with this prior source provided in the July 2009 conference, reference is made to the chemical structure of Figure 1.

Section 4.2 on page 1092 (left column, penultimate paragraph) covers a report about the **clinical trials with S/GSK1349572** and discloses that the "ING112276" trial includes the **co-administration** of an optimal once-daily dose of **this compound and** a fixed-dose **combination of abacavir/lamivudine**. As further revealed from the cited source no. 83, the ING112276 trial is directed to treat HIV-1 (cf. reference list on p. 1097).

Accordingly, the disclosure of **D1** takes away the novelty of the subject-matter of **claims 1 to 5 and 9** of the opposed patent.

With respect to **claims 6 to 8**, it is noted that the term "pharmaceutical composition" according to the opposed patent apparently has a broad meaning, i.e. not necessarily specifying a fixed combination of all three therapeutic agents within the same composition, but also including different pharmaceutical compositions, respectively simultaneous or separately formulated administration forms or separate items as kit of parts (cf. e.g. [0027], [0065] and [0072]).

Therefore, the subject-matter of **claims 6 to 8** of the opposed patent is not novel vis-à-vis D1, either.

2. **Lack of novelty in view of D2**

Document **D2** is a report from September 2009 in a clinical trials review about the dose ranging trial of **GSK1349572 co-administered with** the two NRTI (Nucleoside Reverse Transcriptase Inhibitor) compounds **abacavir/lamivudine** (see main study title and the "official title" in **D2**). The study identified as ING112276 is directed to HIV-1-infected anti-retroviral therapy of naive adult subjects. Again, GSK1349572 was already known to correspond to the compound of formula (I) (cf. **D1**, Fig. 1).

Accordingly, the subject-matter of **claims 1 to 9** is deprived from novelty in view of the disclosure of **D2**.

3. **Lack of novelty in view of D3**

During the XVIII International Aids Conference held on July 18-23, 2010, a report was published, as revealed by the Abstract **D3**, on the combination therapy of **S/GSK1349572 with co-formulated ABC/3TC** (cf. description of the underlying methods of the SPRING-1 anti-HIV trial). This document discloses the interim 16-week analysis from the clinical trial ING112276 (see D2).

The identity of the combined compounds were known: as already noted above with respect to **D1**, the compound S/GSK1348572 was known to correspond to the compound of formula (I) (see again Fig. 1 of D1 depicted above). A further source for identification is document **D12**, where the compound of formula (I) and its identifier

GSK1349572 can be depicted from page 893, further noting that document **D3** is listed as reference no. 4 on p. 894 of D12.

"ABC" is the known abbreviation of abacavir, notably its hemisulfate salt (cf. e.g. **D8**, legends of Table 5a on page 39 and Table 5b on page 40; **D10**, p. 260 left col.), and "3TC" is the known abbreviation of lamivudine (cf. again e.g. **D8**, legends of Table 5a on page 39 and Table 5b on page 40; **D10**, p. 260 left col.).

Accordingly, the subject-matter of all **claims 1 to 9** is not novel vis-à-vis the disclosure by **D3**.

4. **Lack of novelty in view of D4**

Document **D4** constitutes another publication about the **combination**, as anti HIV-1 therapy, of **S/GSK1349572** (i.e. the compound of formula (I); cf. **D1**, Fig. 1) **with ABC/3TC** (corresponding to abacavir and lamivudine; cf. e.g. D1, D8, D10). This document discloses the results from the clinical trial ING112276 (see D2 and D3).

Therefore, also document **D4** anticipates the subject-matter of **claims 1 to 9** of the opposed patent.

VI.
Lack of inventive step (Art. 56 EPC)

*Lack of inventive step in view of **D1, D2, D3 and/or D4***

1. Given the anticipating disclosure of each of the documents **D1, D2, D3** and **D4** (see the observations made in section IV above), the whole claimed subject-matter of the opposed patent self-evidently also lacks an inventive step in view of each of this prior art knowledge.

Moreover, independent from the issue of lack of priority, the claimed subject-matter is not inventive for the following reasons:

*Starting from **D5 as the closest prior art***

2. Already prior to the claimed priority date, Young et al. (**D5**) report in the AIDS Conference of November 2009 about the results of a pilot study of the triple combination of the raltegravir (RAL) combined with abacavir and lamivudine (ABC/3TC) in antiretroviral naïve HIV-1 infected subjects (see title). As mentioned in the "Conclusions" (cf. page 2) and as shown by the data of D5, ABC/3TC + RAL achieved rapid virologic suppression and exhibited potent antiretroviral activity and was well tolerated. The authors of the study conclude that "**the combination of ABC/3TC**, which constitutes the previously well established and pharmaceutically approved nucleoside reverse transcriptase inhibitor (NRTI) dual combination (see e.g. "INTRODUCTION" on p. 3 of D5), **and integrase inhibitors merits further study**".

*Difference and objective technical problem when starting from **D5***

3. The only *difference* of the claimed subject-matter of the opposed patent and the disclosure of D5 is that the integrase inhibitor compound of formula (I) replaces the integrase inhibitor compound raltegravir (RAL) in the triple combination with reverse transcriptase inhibitors abacavir and lamivudine (ABC/3TC) of D5.

The opposed patent does not provide a comparison of triple combinations where the component RAL (raltegravir) would be replaced by the compound of formula (I) (GSK1349572), respectively in association with the two NRTI compounds abacavir (ABC) and lamivudine (3TC). Even less, the opposed patent itself merely provide data on dual combinations (Reference Example; Figs. 1-3), distinct from the experimental details and the positive clinical trial observations on the triple combination RAL/ABC/3TC of the closest prior art D5 considered here. Even in the embodiments of the application dealing with dual combinations, no example or indication on the effectiveness with lamivudine (3TC) is given, let alone a potential synergistic contribution thereof (cf. again Reference Example; Figs. 1-3).

Thus, the only contribution over the art by the technical information provided in the opposed patent could be seen in dual combinations the compound of formula (I) (GSK1349572) with various other known anti-HIV compounds. From a number of synergistic combinations, including stavudine, abacavir, efavirez, nevirapine, lopinavir, amprenavir and enfuvirtide (see [0087] of the opposed patent), abacavir was finally chosen for the subject to be claimed. Any contribution or effect by way of

lamivudine was neither shown nor contemplated whatsoever. To the contrary, D5 did actually demonstrate an effective anti-HIV efficacy by way of potent antiretroviral activity and rapid virologic suppression in human pilot study trials.

Accordingly, the *objective technical problem* can merely be seen in the provision of an *alternative* anti-HIV-1 combination of an HIV-integrase inhibitor (INI/INSTI) with the 2NRTIs abacavir(ABC)+lamivudine(3TC).
However, *even if* the objective problem, despite and contrary to the aforementioned reasonable assumption due to a lack of showing on the opposed patent, could be formulated as the provision of an *improved* triple combination of an HIV-integrase inhibitor (INI/INSTI) with abacavir(ABC)+lamivudine(3TC), the following observations would still fully apply.

Incentives and suggestions to replace raltegravir by the compound of formula (I)

4. Integrase inhibitors such as raltegravir are one of the newest classes of antiretroviral agents and at the priority date of the opposed patent raltegravir was the only approved integrase inhibitor for the treatment of HIV-infected patients. However, the search for new integrase inhibitors with different mechanisms of actions and resistance profiles was already encouraged (see Abstract of D1).
Following the earlier developed raltegravir but still prior to the claimed priority date, it is established that the compound of formula (I) became known as a new integrase inhibitor from the patent family represented by WO2006116764A (**D6**) and embodied by the issued patent JP4295353B2 (**D6A**).
Specifically, this document does disclose the new integrase inhibitor, which corresponds to the present compound of formula (I)=dolutegravir, individually in Example Y-3 (page 116 of WO'764) and does claim this compound specifically by way of claim 32 in WO'764 (cf. page 267, third listed compound). In particular, precisely this integrase inhibitor was **further individualized** by its specific claiming as one out the prior larger list (claim 32 of D6) in the issued patent derived from the D6 patent family, notably by way of **claim 36** in the granted patent **JP'353 (D6A)** (cf. English partial translation, **D6B**). This allows a reasonable presumption that the correspondingly individualized compound is the lead candidate drug for further development, namely the "formula (I)" compound (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benylamide.

Patent document D6/D6A further teaches that the compound disclosed therein exhibit very strong integrase inhibitory activity. D6/D6A further teaches that the newly found integrase inhibitors **lend themselves** for a **combined therapy especially with reverse transcriptase inhibitors like the explicitly mentioned 3TC** (previously known and therapeutically established as lamivudine), and this knowledge even constituted the very motivation to develop such new HIV integrase inhibitor compound (cf. [0002] on page 1 of D6). Consistent with this goal, it is explicitly mentioned in D6/D6A that "the present compound" is useful in joint use therapy by being combined with a reverse transcriptase inhibitor. See page 78 (second paragraph) of D6:

In addition, the present compound may be used in joint use therapy by combining an anti-HIV drug having the different action methanism such as a reverse trascriptase 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.

This statement reflects the general and reasonable expectation that when active compounds are combined where the respective active represent different action mechanism, synergism may be achieved.

As noted, due to the fact that the compound of formula (I) was individually synthesized and claimed, all the more by its individual claiming in already prosecuted and granted patent claims by way of D6A, the importance of this compound, also in combination with reverse transcriptase inhibitors like 3TC (lamivudine), was clearly indicated.

Accordingly, D6/D6A provides a clear incentive and suggestion to use the compound of formula (I) as the very potent HIV integrase inhibitor candidate in combination with reverse transcriptase inhibitors. It is thus more than evident to replace the meanwhile established integrase compound raltegravir (RAL) in the later successfully proven triple combination with ABC/3TC of D5. The skilled person was even more prompted to do so by the indication in D6 itself that such a combination with reverse transcriptase inhibitors, owing to the different action mechanisms, may lead to synergism. A further suggestion to do so is based on the fact that a combination with the established lamivudine compound 3TC is explicitly addressed as a desirable goal

of D6 (see again [0002] on page 1 of D6), which is well in line with the concept of the pilot study of D5.

And in further confirming consistency, the skilled person will take notice of the conclusion in D5 that a combination of ABC/3TC **"and integrase inhibitors**" in general merits further study (see again "Conclusions" on page 2 of D5). This is a motivation of its own, and thereby the skilled person is even further encouraged to use and test a corresponding further triple combination where raltegravir is replaced by another integrase inhibitor. With the particularly highlighted integrase inhibitor of D6A (individualized by the specific claim 36) that follows the earlier one raltegravir, the skilled person had a reasonable expectation that also a combination of this compound with ABC/3TC would solve the present underlying problem.

Following these incentives, suggestions and reasonable expectations from D5 and D6/D6A, the skilled person did directly arrive at the subject-matter of claims 1 to 9 without the exercise of an inventive step.

Further prior art suggestions to replace raltegravir by the compound of formula (I)

5. Although the observations outlined under item 4 above do already substantiate lack of inventive step based on D5 and D6 alone, for the sake of completion and as a further substantiation of its own it will be shown that the prior art contains further suggestions to replace raltegravir by the compound of formula (I).

To this end, it is submitted that document **D2** is well in line with the scenario and considerations already forecasted by the skilled person's combination of D5 and D6 as demonstrated above. Indeed, D2 confirms the reality of what was suggested already by D5 and D6. According to the study outline in D2 of September 2009, the developed drug candidate GSK1349572 in fact shall be tested as the selected integrase inhibitor component (where the function is indicated by the keywords on page 4 of D2) in clinical trials of HIV-1 infected patients in the triple combination with the two reverse transcriptase inhibitors abacavir and lamivudine. GSK1349572 was already known to correspond to the compound of formula (I) (cf. **D1**, Fig. 1).

Furthermore, since the sponsors and collaborators of the study – GlaxoSmithKline (GSK) and Shionogi – had been the co-applicants of D6, there was an immediately evident presumption that GSK1349572 stands for the integrase inhibitor selected

from D6. As already noted above, the individual claiming in D6A out of a longer list of specified compounds points to this selection.
As the result of such straightforward considerations, the triple combination of this GSK1349572 = (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benylamide (i.e. the compound of formula (I)) with the NRTIs abacavir and lamivudine (ABC/3TC) is directly obtained without any further information being required.

Thus, the subject-matter of claims 1 to 9 of the opposed patent does not involve an inventive step all the more if D2 is taken into account, either alone or in conjunction with D6/D6A.

6. A further prior art suggestion is established by way of document **D7**. The authors report here about the pharmacokinetics and safety of compound **S/GSK1349572 as "the next-generation HIV integrase inhibitor**", having potent *in vitro* anti-HIV activity and *in vitro* resistance profile different from those of other integrase inhibitors (cf. title and abstract).
Also from D7, **improvements** of this next-generation HIV integrase inhibitor **compared to raltegravir and raltegravir-containing treatment regimes** can be **expected**, as this document explains that this compound S/GSK1349572 (cf. page 254, emphasis added):

- "is designed to **retain activity against raltegravir**- and elvitegravir-**resistant HIV**"
- "was selected for clinical trials because nonclinical studies demonstrated a favorable safety profile, pharmacokinetics (PK) supporting **once-daily dosing**, and the **potential for activity against raltegravir- and elvitegravir-resistant HIV**", and
- has an **IC50 value of 0.51 nM** and a protein-adjusted IC90 value of 0.064µg/ml.

The skilled person immediately realizes that precisely this compound is already subject to the triple combination clinical study of D2 discussed above. And for the same reasons already demonstrated in conjunction with D2 above, the skilled person could easily link the compound denoted S/GSK1349572 with its corresponding chemical/structural identity.

Thus, the subject-matter of claims 1 to 9 of the opposed patent does not meet the requirements of Art. 56 EPC all the more if D7 was taken into account.

Further indications in the prior art on expectable improvements when combining newly provided integrase inhibitor with abacavir/lamivudine (ABC/3TC)

Again, although the above observations do already substantiate lack of inventive step based on D5 and D6 alone, and/or in consideration of D2, the following is added merely for the sake of completion.

7. Virus resistance against anti-HIV drugs is a common problem in anti-HIV treatment regimes. This is for instance addressed and reflected repeatedly in the anti-HIV/AIDS Guidelines (**D8**). As the Guidelines were updated in this 2009 version of D8 (note: the passages marked in yellow originally represent new information in this updated version), integrase was newly identified as a target for resistivity considerations (cf. page 9, especially the passage subtitled with "Genotypic Assays"; page 11, 2nd para). Accordingly, within such virus-resistance considerations already the availability of second-line drugs of the integrase inhibitor class – besides the then approved anti-HIV drug raltegravir – was of great interest (page 11, 6th para. of D8).
The 2009 Guidelines already report about the anti-HIV community having started the use of raltegravir as the first integrase inhibitor in combination with the dual NRTIs abacavir/lamivudine (cf. page 46, 2nd paragraph under the subtitle "INSTI-based regimen (INSTI + 2 NRTIs); Table 5b on page 40). The section of D8 on page 46 under the title "DUAL-NRTI OPTIONS AS PART OF INITIAL COMBINATION THERAPY" discloses that dual NRTIs shall be considered in combination with an integrase inhibitor (INSTI), besides a consideration of a combination with an NNRTI or a PI.

Accordingly, D8 represents an additional incentive to develop another integrase inhibitor, further to raltegravir and its already indicated anti-HIV activity when used in combination with abacavir/lamivudine (ABC/3TC). Already the demand expressed in D8 to provide a second-line drug within the same class to address resistivity issues is a clear motivation to make use of new integrase inhibitors when available.

Without doubt, the integrase inhibitor disclosed in D6 and individualized/highlighted by D6A meets this demand. Accordingly, D8 demonstrates the skilled person's motivation to use the second generation drug disclosed and individualized in D6A,

which corresponds to the present compound of formula (I), as a new and potent member of the integrase inhibitor class, and use it in the anti-HIV triple combination with the dual NRTIs combination abacavir/lamivudine instead of the only previously approved integrase inhibitor raltegravir, yet with the same treatment principle.

8. Document **D9** represents another promising springboard for the person skilled in the art. Similar to D5, it deals with an actually effective therapeutic use of the raltegravir (RAL)+2NRTI-based combination regimen. **D9** indicates this triple combination as a good option in HIV-infected patients in a relevant clinical setting (HIV-infected patients undergoing solid organ transplantations, SOT), cf. title and last sentence in the Abstract of D9.

Specifically, in a substantial part of the treated patient groups, as can be seen from patient nos. 1, 4-6, 9, 12 and 13 listed in Table 2, raltegravir was combined with the two NRTI compounds abacavir (ABC) and lamivudine (3TC). With the data available then by this first experience of a triple combination of integrase inhibitor + 2 NRTIs, the authors conclude with a recommendation to further pursue such triple combination regimen in the underlying relevant context of HIV-infected patients.

Thus, in confirmation and supportive for the above evaluation, with a similar rationale it was then obvious to replace the prior raltegravir integrase inhibitor by the newly developed integrase inhibitor compound disclosed in D6 and in particular the compound of formula (I) individualized especially in D6A.
Accordingly and analogous to the observations above, the skilled person was motivated to use the next-generation INSTI compound of formula (I) (S/GSK1349572) in the triple combination with the NRTIs abacavir (ABC) and lamivudine (3TC) disclosed in D9, thereby again arriving at the subject-matter of **claims 1 to 9** of the opposed patent without requiring an inventive step.

9. Given the failure to be entitled to the claimed priority, knowledge revealed by further prior art documents could further be taken into account.

9.1 **D10** is similar to D5 as it represents the full paper of the pilot study report briefly summarized already in the conference report of D5. Accordingly **D10** confirms the positive evaluation of the combination of **raltegravir+abacavir/lamivudine** in anti-retroviral naive, HIV-1-infected patients (cf. title and "purpose" in the Abstract on page

260). According to the "conclusions" in the Abstract and correspondingly in the statement on p. 267, it was found that

> "*abacavir/lamivudine+raltegravir was effective and generally well-tolerated over 48 weeks with modest changes in fasting lipids.*"

9.2 In **D11** (Johns et al.) further report about the benefit of S/GSK1349572 (whose structural identity with the compound of formula (I) is shown on page 5) over the use of raltegravir in terms of better patient adherence/compliance, low PK variability, antiviral activity and superior in vitro resistance profile with potential for higher genetic barrier to resistance (page 2 under the subtitle "*S/GSK1349572: Attributes of a Next-Generation INI*").

In addition, **D11** teaches on page 2 under the subtitle "*S/GSK1349572 is a Broadly Potent HIV-Antiviral and Synergistic or Additive with Approved Anti-HIV Drugs*" that this compound S/GSK1349572 (identified by its formula) is synergistic or additive with approved anti-HIV drugs, including NRTIs.

Therefore, the skilled person was further prompted and motivated by **D11** to replace the prior (first-generation) integrase inhibitor raltegravir in the INSTI-based regimen with the 2NRTIs combination abacavir/lamivudine, respectively (cf. **D5**, **D9, D10**). Given the potential resistivity issues of raltegravir, the skilled person would do so with the reasonable expectation of success of an improved anti-HIV-1 therapy, to thereby solve the underlying problem.

Accordingly, starting from the known INSTI + ABC/3TC NRTI triple combination (**D5, D9, D10**) and taking account of the teaching and suggestion from **D11**, the skilled person would have obviously chosen the "next generation" triple combination with the compound S/GSK1349572 of formula (I) replacing raltegravir, and thus would have obviously arrived at the subject-matter of defined in **claim 1** of the opposed patent.

9.3 The documents reporting about the benefits of using the compound of formula (I) (GSK1349572) over raltegravir can be further continued, for instance by referring to the following additional documents:

For instance from document **D12**, which not only directly reports about the high potency of the HIV-integrase inhibitor action (see bottom at page 893 and top of page

894), but by reference to the cited literature references on p. 894 (e.g. no. 7) further report about the clear therapeutic benefits of avoiding the problem resistance, which was already then known to be associated with the first-generation INSTI compound raltegravir. This document also cites the patent family of **D6** (reference no. 1).

Further, **D13** (Underwood et al.) suggests using the next-generation INSTI compound S/GSK1349572 in previous RAL-based therapies (see the conclusions at the bottom right column).

Again and analogous to the considerations already made before when starting from the known RAL+ABC/3TC triple INSTI+2NRTIs combination, the disclosure of each of **D12 and D13** about the further development of HIV integrase inhibitors and the beneficial replacement of raltegravir by the compound of formula (I) (S/GSK1349572) in the previous RAL+ABC/3TC combination, has obviously led the skilled person to the subject-matter of the opposed patent.

In other words, also each of **D12 and D13** prompted the skilled person to replace raltegravir in the previous disclosed triple combination of anyone of **D5, D9** and **D10**, respectively.

10. As already demonstrated, the features of the dependent claims are known from the prior art.

For instance, the skilled person also knew that the sodium salt recited in **claim 2** is the suitable pharmaceutical acceptable salt form of the compound of formula (I), as revealed e.g. from **D1** (Fig. 1) and **D11** (page 5).

Regarding **claim 3**, the skilled person knew that the hemi-sulfate salt is the commonly used pharmaceutically acceptable salt of abacavir, abbreviated as ABC (cf. page 260, left column of **D10**).

For likewise reasons already outlined before, the features of **claims 4 to 9** were known, too.

In summary, the subject-matters of **claims 2 to 9** are not further distinguished from the established prior art, and hence its subject-matter lacks novelty and inventive step for the same reasons as put forth for claim 1.

VII.
Conclusion

Since the claimed subject-matter is neither novel nor inventive over the established prior art, the request to revoke the patent in total is justified. In addition claims 2 and 4-9 do violate Art. 123(2) EPC.

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Enclosures:
D1 to D13