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Datasheet for the decision of 2 October 2024

Case Number: T 1698/21 - 3.3.07

Application Number: 16187411.0

Publication Number: 3127542

IPC: A61K31/5365, A61K31/52, A61P31/18

Language of the proceedings: EN

Title of invention:
ANTIVIRAL THERAPY

Patent Proprietor:
VIIV Healthcare Company

Opponents:
Cooke, Richard
Sandoz AG
Teva Pharmaceutical Industries Ltd
STADA Arzneimittel AG

Headword:
ANTIVIRAL THERAPY/VIIV Healthcare Company

Relevant legal provisions:
EPC Art. 123(2), 76(1), 83, 87(1), 56

Keyword:

Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Priority - validity of priority date (yes)
Inventive step - main request (yes)

Decisions cited:

G 0001/22, G 0002/21

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Case Number: T 1698/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 October 2024

Appellant: (Opponent 1)	Cooke, Richard Elkington and Fife LLP Patents Department 3-4 Holborn Circus London EC1N 2HA (GB)
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Appellant: (Opponent 2)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Appellant: (Opponent 3)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Appellant: (Opponent 4)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)

Respondent: (Patent Proprietor)	VIIV Healthcare Company 251 Little Falls Drive Wilmington, DE 19808 (US)
Representative:	Wilkinson, Johanna Elise GSK Legal & Compliance - Global Patents 79 New Oxford Street London WC1A 1DG (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 July 2021 rejecting the opposition filed against European patent No. 3127542 pursuant to Article 101(2) EPC.**

Composition of the Board:

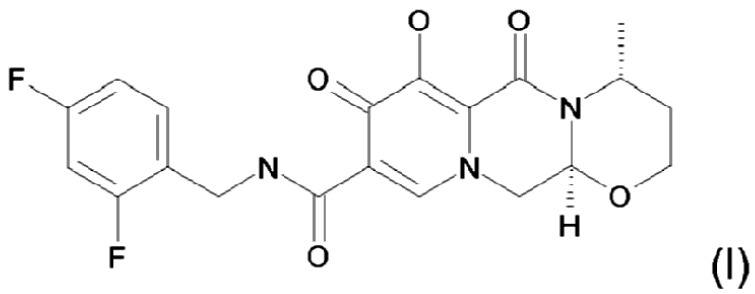
Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 3 127 542 B1 was granted on the basis of a set of 10 claims.

Independent claim 1 as granted read as follows:

"1. A combination comprising a compound of formula (I)



(I)

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

II. Four oppositions were filed against the granted patent under Article 100 (a), (b), (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division to reject the oppositions.

IV. The documents cited during the opposition proceedings included the following:

D1: Clinical Trial NCT00951015 (July 2009)
D1a: Clinical Trial NCT00951015 (January 2010)
D11: US 7,511,037 B2
D13: Guidelines for the use of ARVs Agents in the treatment of HIV-1 infected adults and adolescents
D14: Garvey et al. "The Naphthyridinone GSK364735 Is a Novel, Potent Human D14 Immunodeficiency Virus Type 1 lntegrase Inhibitor and Antiretroviral", Antimicrobial Agents and Chemotherapy, Mar. 2008, p. 901-908
D15: ISENTRESS (raltegravir) Tablets; patient information leaflet; published by the FDA in July 2009
D17: WO 2006/116764 A1
D18: Assignment from Mark RichardUnderwood dated 31 January 2011
D19 Assignment from Mark Richard Underwood dated 31 January 2011
D20: Kobayashi et al., "In Vitro Antiretroviral Properties of S/GSKl349572, a Next Generation D20 HIV Integrase Inhibitor", Antimicrob. Agents Chemother., Vol. 55(2), Feb. 2011, p. 813- 821, published ahead of print on November 29, 2010
D36: Young et al, EACS, 2009
D40: JP4295353
D50: Summary of product characteristics for Triumeq
D51: Trembley et al., Value in Health Regional Issues 16 (2018) 74-80
D52: Johns et al, J. Med. Chem. (2013), 56, pages 5901-5916
D53: Assignment document
D54: Patent consent form for ING 112276
D57: Peterson, John J. et al., "Nonlinear Blending: A Useful General Concept for the Assessment of Combination Drug Synergy" Journal of Receptors and Signal Transduction, Vol. 27, 2007

V. According to the decision under appeal, the formal entitlement to priority has been sufficiently established in view of D53.

The requirements of Article 76(1) and 123(2) EPC were also fulfilled for claims 1 and 3 as granted.

The requirements of sufficiency of disclosure were met and the claimed subject-matter was novel over D1, D1a D28, D29, D34 and D20.

With regard to inventive step, D11, D14 or D15 were all suitable as closest prior art. The problem was defined as the provision of an alternative synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV. The claimed solution was not obvious. When starting from D36, the problem was the provision of combination of abacavir and an integrase inhibitor having a synergistic effect. The claimed solution was neither obvious.

VI. Opponent 01 (hereinafter appellant 01), opponent 02 (hereinafter appellant 02), opponent 03 (hereinafter appellant 03) and opponent 04 (hereinafter appellant 04) filed an appeal against said decision.

VII. With its statement setting out the grounds of appeal dated 30 November 2021, appellant 03 submitted the following items of evidence:

D60: Further partial translation of JP 4295353 B2
D61: EMA Scientific Discussion of Raltegravir (2008), pages 1 to 6

VIII. With its reply to the statements of grounds of appeal dated 31 March 2022, the patent-proprietor (hereinafter

the respondent) filed auxiliary requests 1 and 2, and submitted the following evidence:

D62: Declaration of Arlene Cannon

IX. A communication from the Board, dated 6 September 2023, was sent to the parties. In it, the Board expressed its preliminary opinion that the main request appeared to meet the requirements of Articles 76(1), 123(2) and 83 EPC, and was novel; inventive step starting from D11, D14, D15 and D36 was also assessed. The Board defined the problem over these documents as respectively:
- the problem over D11 was the provision of an alternative synergistic combination for treating HIV
- the problem over D14 appeared to be the provision of an improved synergistic combination for treating HIV
- the problem over D15 or D36 appeared to be the provision of a synergistic combination for treating HIV.

The Board did furthermore not see any reason to question the validity of the priority.

X. Oral proceedings took place on 2 October 2024. For further details concerning the oral proceedings, reference is made to the minutes thereof.

XI. The arguments of the appellants may be summarised as follows:

Main request - Added Matter

According to appellant 02, the original application did not encompass combinations of the compound of Formula (I), i.e. dolutegravir, with salts of the second active

agent, i.e. with pharmaceutically acceptable salts of abacavir.

Main request - Sufficiency of disclosure

According to appellant 02, the opposed patent did not disclose the suitability of the combination of dolutegravir and abacavir for any therapeutic application as claimed in the first therapeutic use claim 4 of the opposed patent.

Validity of the priority

Appellant 04 considered that there was no evidence on file that the right of priority had been assigned before the filing date of the contested patent, in view of the contradictory information contained in D18/D19 and D53, which in fact were mutually exclusive. Consequently, the priority was not valid and D20 was relevant for novelty.

Main request - Inventive step

According to appellant 01, the problem over D11 was the provision of an alternative composition. The patent could not encompass further technical effects such as a reduced toxicity or a suitability for a once- a day-dosing; the passages cited by the respondent with regard to these effects were simply statements and could not form the basis of such new effects. The problem of increased potency of the integrase inhibitor was furthermore inconsistent with the arguments that the synergistic effect of the claimed combination was not predictable. The claimed solution was obvious in view of D17 which disclosed dolutegravir, i.e. the compound of Formula (I), in particular since no

antagonism between an integrase inhibitor and abacavir was observed in D14 or D15. Abacavir was indeed synergistic with any integrase inhibitor in general, and it would have been obvious to replace the integrase inhibitor of D11 by dolutegravir known from D17, this even in the case of a possible synergistic effect.

In its written submissions, appellant 01 also considered D14 or D15 as closest prior art. As for D11, the distinguishing feature was the use of dolutegravir as the HIV integrase inhibitor. The problem was defined as the provision of an alternative composition and the solution was obvious, even if the problem had to be defined as the provision of an alternative synergistic composition.

According to appellant 02, the effect shown by Figure 1 of the patent could not be a stronger effect than in D11 and this effect was even questionable in view of the few points analysed in said Figure 1, in particular in view of the absence of any analysis for higher concentrations of abacavir. The problem over D11 was the provision of an alternative combination with abacavir, and for the lower concentrations of abacavir the provision of an alternative synergistic composition with abacavir; the problem was the provision of an alternative synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV. The solution was obvious in view of D11, D17, D14 and D15, since the skilled person would check if there existed any antagonism, and would have selected any combination that might be synergistic and would have arrived inevitably at the solution to use dolutegravir.

According to appellant 02 the same conclusions applied when starting from D14 or D15 as closest prior art. It

also considered D36 as a starting point, and defined the problem over D36 as the provision of a synergistic combination of abacavir with an INSTI (integrase inhibitor). The claimed solution was obvious in view of D17/D40.

Appellant 03 could not identify any improvement over D11. The claimed solution was obvious in view of D11, D14, D15, D17 and D61. All these documents showed a clear trend in the prior art that abacavir formed a synergistic combination with any integrase inhibitor. Accordingly, the use of dolutegravir could not involve an inventive step.

D36 was a better closest prior art than D11 for appellant 04. In any case, Figure 1 of the patent was not relevant, and did not disclose which dose of abacavir was useful and which effect was measured; it was not possible to draw any conclusion from Figure 1. The isobologram contained in the contested patent (Figure 1) did furthermore not allow any conclusion to be drawn regarding an actual synergistic effect of the combination of dolutegravir and abacavir in the real treatment of humans. The problem could only be the provision of an alternative composition, since no effect was shown. The claimed solution was obvious in view of D17 or D40 in which dolutegravir was singled out in the claims.

XII. The arguments of the respondent may be summarised as follows

Main request - Added Matter

The application as filed provided a direct and unambiguous disclosure of a combination of dolutegravir

and abacavir, wherein both of these therapeutic agents might be present in the form of a pharmaceutically acceptable salt. This objection was therefore not convincing.

Main request - Sufficiency of disclosure

The claims of the patent were directed to combinations of known compounds. Paragraphs [0046] and [0047] of the patent explained how the claimed compounds may be prepared. The patent further contained experimental data, in Figure 1, which evidenced the synergistic interaction between the compound of formula (I).

Claim 4 was a first medical use claim which referred to the novel and inventive drug combination specified in claim 1. If a specific product had not previously been disclosed in a therapeutic context, it was legitimate to formulate a "first medical use" claim which referred generally to the product at issue for use as a medicament.

Validity of the priority

The original PCT application from which this patent is derived, PCT/US2011/022219, named GlaxoSmithKline LLC (GSK LLC) as the applicant for all designated states except for the US. It named Mark Underwood as inventor and applicant for the US only. This PCT application claimed priority from US 61/298,589, which named Mark Underwood as applicant. D53 was an assignment executed by Mark Underwood. It assigned to GSK LLC all relevant rights, including the right to claim priority (see last 2 lines of page 1 of D53). The right to claim priority was therefore properly and explicitly assigned to the correct applicant named on the PCT request form.

Main request - Inventive step

The problem over D11 was the provision of a synergistic combination for treating HIV having an increased potency on the integrase enzyme. Figure 1 was relevant for showing an effect, and showed that the combination of the two drugs had an overall synergistic effect; D20 showed that dolutegravir had the strongest potency among the known integrase inhibitors. Starting from the cited prior art the skilled person had no reasonable expectation of success that the claimed combination would have a synergistic effect, and this effect could not have been predicted. Moreover, not all integrase inhibitors were able to provide a synergistic effect, in particular with abacavir. The claimed solution was therefore not obvious.

The problem over D14 was to provide a drug combination which represented an improved synergistic combination for treating HIV, which had a pharmacokinetic profile suitable for once daily dosing, which contained an integrase inhibitor which had reduced in-vivo toxicity, and which contained an integrase inhibitor which had increased potency. The claimed solution was not obvious.

The problem over D15 or D36 was the provision of an improved synergistic combination, and the claimed solution was also not obvious over these documents.

XIII. Requests

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

The respondent requested that the appeals be dismissed such that the patent was maintained as granted (main request), or, as an auxiliary measure, that the decision under appeal be set aside and the case be remitted to the opposition division for consideration of auxiliary requests 1 and 2 filed with letter of 31 March 2022, or that the patent be maintained on the basis of one of these auxiliary requests.

Reasons for the Decision

1. Main request - Added Subject-matter

1.1 According to appellant 02, there was no basis in the original application for combinations of dolutegravir, i.e. the compound of Formula I, with salts of the second agent, namely abacavir.

1.2 Claim 1 of the patent application EP 16 187 411.0 discloses directly the combination of dolutegravir and "abacavir or a pharmaceutically acceptable salt thereof".

The requirements of Article 123(2) EPC are therefore met.

1.3 A combination of dolutegravir and abacavir is derivable directly and unambiguously from the subject-matter of claims 1 and 2 of the parent application published as WO 2011/094150 (application EP 11 737 484.3) or from page 6, lines 16 to 18.

With regard to the salts of abacavir, the description of the parent application published as WO2011/094150 makes an explicit reference to the salts of abacavir on page 9, lines 22-26, namely that "the present invention features combinations, methods of treatment, and pharmaceutical compositions as described above wherein one or more therapeutic agents are a pharmaceutically acceptable salt of said therapeutic agents, for example, abacavir hemisulfate,...". This passage constitutes an explicit and valid basis for the presence of salts of abacavir in the claimed combination. The same passage is also included in the other earlier application EP 15 164 931.6 and in the patent application (see paragraph [0043]).

Consequently, the main request meets also the requirements of Article 76(1) EPC.

2. Main request - Sufficiency of disclosure

2.1 The sufficiency of disclosure of the claimed invention has been objected to by appellant 02 in view of claim 4 of the main request, since the patent does not disclose the suitability of the combination **for any therapy**.

Claim 4 of the main request reads:

"4. A combination according to any of claims 1-3 for use in medical therapy".

2.2 This claim has been drafted in the form of a first medical use type claim (Article 54(4) EPC). The EPC allows a purpose-limited substance claim stating a general therapeutic purpose, in particular when a known compound is for the first time proposed and claimed for

use in therapy. Hence, the scope of this claim is not the product for use in any specific medical therapy **but for a generic use in medical therapy as defined in Article 54(4) EPC.**

Since both products are known in the field of therapy, their combination is obviously suitable for such use and the requirements of sufficiency of disclosure are met.

3. Validity of the priority

3.1 Appellant 04 challenged the validity of the priority, and submitted that D20, which was published after the priority date of the contested patent, would consequently become relevant for novelty under Article 54(2) EPC.

3.2 Documents D18, D19, D53 and D62 were mentioned in this context by the parties.

3.2.1 D53 is a signed assignment from Mark Richard Underwood wherein the whole rights relating to the application US 61/298589 were assigned and transferred to Glaxosmithkline LLC. The assignment was signed on **20 January 2011**, hence before the filing date of 24 January 2011 of the PCT application corresponding to the contested patent.

3.2.2 D18 is identical to D19 and is an assignment document comprising the same assignment as in D53 but signed on **31 January 2011**, hence after the filing date of the PCT application on 24 January 2011. The document makes reference to the priority application US 61/298,589 and to the further PCT international application PCT/

US2011/022219 corresponding to the published application WO 2011/0894150.

3.2.3 D62 is a declaration signed by Arlene Cannon, who was employed by GSK as a US Patent Formalities Manager in 2011, and provides her account of the relevant GSK standard operating procedures at the time. It explains in particular that the standard practice at that time was to execute two assignment documents, a first assignment document which was executed to ensure that the right to claim priority was properly transferred before the filing date of the PCT application. To that end, it was necessary to have that first assignment document prepared and executed before the PCT application number was available, and then to arrange for a second assignment document to be executed by the inventor shortly after the PCT application was filed, which made reference to the PCT application number.

3.3 The Board notes indeed an inconsistency between the information provided by documents D18/D19 and D53. According to documents D18 and D19, the transfer of the priority right was conducted on **31 January 2011**, after the filing date of the patent while, according to the assignment D53, the transfer of the priority right was already effected on **20 January 2011**. The question is whether this could result in a finding that the priority has not been validly transferred.

According to G 1/22, there is a rebuttable presumption under the autonomous law of the EPC that the applicant claiming priority in accordance with Article 88(1) EPC and the corresponding Implementing Regulations is entitled to claim priority (cf. Headnotes of G 1/22). Such a presumption implies a reversal of the burden of proof and it is therefore up to the opponents to prove

that the applicant cannot validly claim priority, and doubts, even serious ones, cannot suffice. In the present case, the mere inconsistency between two documents, for which D62 provides a credible explanation, is no proof that the priority has not been validly claimed nor does it cause serious doubts concerning the transfer.

In the Board's view, it in fact appears convincing that the priority has been validly transferred on 20 January 2011 in view of document D53 and the evidence provided in D62. Document D62 gives a credible explanation for the existence of the two assignments, as disclosed in its points 4-8.

Hence, the Board does not see any reason to question the validity of the priority and document D20 is not relevant under Article 54(2) EPC for the assessment of novelty.

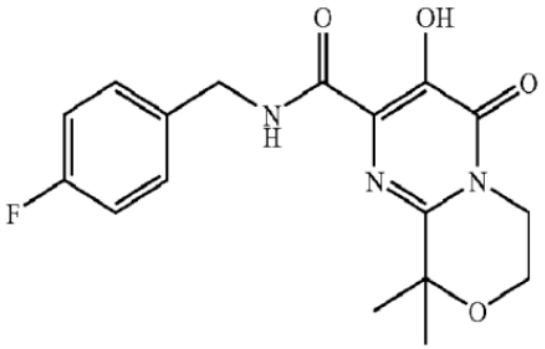
4. Main request - Inventive step

4.1 The claimed invention relates to a combination of a HIV integrase inhibitor, i.e the compound of formula(I) also known as GSK1349572 or dolutegravir, with abacavir, a reverse transcriptase inhibitor.

4.2 The opposition division considered D11, D14 and D15 as equally possible starting points for the assessment of inventive step, since they all relate to the synergistic combination of abacavir with an integrase inhibitor. Appellants 02, 03 and 04 also rely on document D36 as possible closest prior art.

4.2.1 D11 discloses the synergistic combination of an inhibitor of HIV integrase having a bicyclic pyrimidone

structure with *inter alia* abacavir. Example 19 of D11 (column 185) was cited by the opposition division in its decision and discloses a compound having a close structure to dolutegravir:



In columns 75-76 (see in particular col.75 lines 40-53 and Table 4), D11 states that abacavir shows synergistic effects in combination with the compound of example 19 at all effective levels and molar ratios; Tables 4-8 show a great number of possible combinations with the compound of example 19. The following is an extract from Table 4 regarding the combination with abacavir:

TABLE 4-continued

Two-Drug Combinations using Example 19 and Nucleoside Reverse Transcriptase Inhibitors.

Molar Ratio	Combination Indices at % HIV Inhibition[b] (Confidence Interval)		
(EC_{50} Ratio)[a]	50%	75%	90%
Abacavir			
1:30 (1:1)	0.68 (0.59, 0.76)	0.67 (0.56, 0.79)	0.67 (0.49, 0.84)
1:75 (1:2.5)	0.87 (0.77, 0.97)	0.74 (0.63, 0.85)	0.63 (0.50, 0.77)
1:12 (2.5:1)	0.86 (0.76, 0.96)	0.82 (0.68, 0.96)	0.79 (0.58, 0.99)

D11 does not disclose the claimed compound of formula I, i.e dolutegravir.

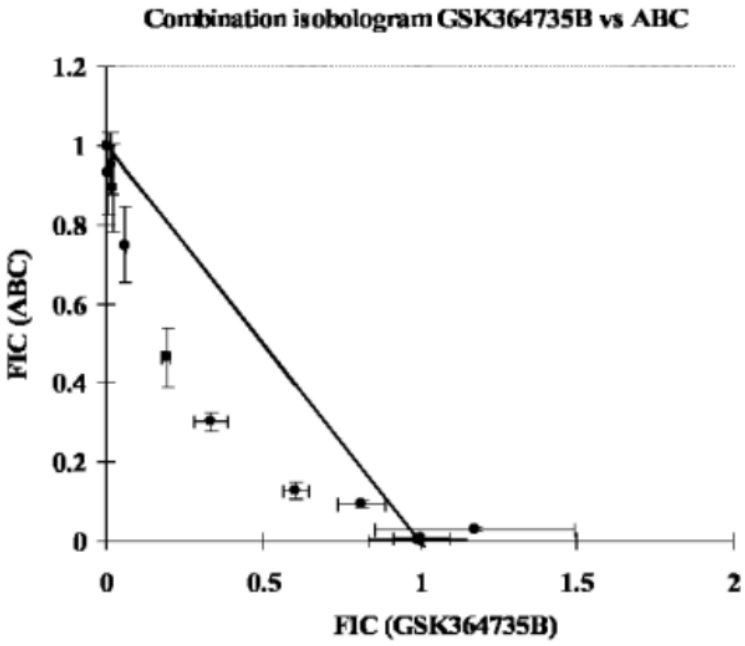
4.2.2 D14 relates to a synergistic combination of GSK364735, **an HIV Type 1 integrase inhibitor different from dolutegravir**, with abacavir (see Fig.1, Table 3, Figure 5).

TABLE 3. Summary of results from combination studies of GSK364735 and approved antiretrovirals[a]

Compound	Deviation from additivity			Interaction with GSK364735
	Average	SE	P (t test)[b]	
GSK364735	−0.013	0.035	0.357	Additive
NRTIs				
Zidovudine	−0.388	0.016	3.4E-08	Synergistic
Stavudine	−0.064	0.034	0.051	Additive
Dideoxycytosine	0.063	0.060	0.159	Additive
Dideoxyinosine	−0.162	0.062	0.0002	Synergistic
Abacavir	−0.111	0.039	0.010	Synergistic
3TC	−0.315	0.027	4.20E-06	Synergistic
Emtricitabine	−0.009	0.062	0.442	Additive
Tenofovir	−0.092	0.030	0.008	Synergistic
NNRTIs				
Efavirenz	−0.006	0.051	0.452	Additive
Nevirapine	−0.108	0.032	0.004	Synergistic
Delavirdine	−0.144	0.027	0.00036	Synergistic
PIs				
Indinavir	0.092	0.072	0.117	Additive
Lopinavir	−0.029	0.047	0.277	Additive
Nelfinavir	−0.239	0.051	0.0027	Synergistic
Ritonavir	0.050	0.049	0.169	Additive
Amprenavir	0.049	0.031	0.079	Additive
Saquinavir	0.025	0.054	0.327	Additive
Atazanavir	−0.058	0.072	0.223	Additive
Fusion inhibitor				
Enfuvirtide (Fuzeon)	−0.197	0.047	0.003	Synergistic

[a] Average values and standard errors are from at least three determinations.
[b] P is the probability that the deviation from additivity is equal to zero.

The synergistic effect of the combination abacavir/ GSK364735 disclosed in D14 is shown by the following isobologram (see Figure 5 of D14 on page 907):



4.2.3 D15 relates to Insentress®, a medicament based on **raltegravir** as integrase inhibitor. This document mentions further on page 12 that "additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide" (cf. par. "Antiviral Activity in Cell Culture").

This document does not specify whether the association of raltegravir and abacavir provides a synergistic effect, and does not relate to dolutegravir. For this reason, D15 appears to be less relevant compared to the

other documents considered as possible starting point for the assessment of inventive step.

4.2.4 D36 is a pilot study of a tri-therapy combination of **abacavir/ lamivudine (ABC/3TC) and raltegravir (RAL, integrase inhibitor)** in naive HIV-1 infected subjects. The study mentions that the combination achieved a rapid virologic suppression and merits further study (see Conclusions on page 2). **The document relates to a tri-therapy and does not mention any synergistic effect, or a possible combination with dolutegravir** or replacement therewith in the disclosed combination.

4.2.5 The Board notes that **the distinguishing feature between the claimed subject-matter and any of the cited documents is always the presence of the integrase inhibitor dolutegravir.** In the Board's view, the closest documents appear to be documents D11 and D14; the assessment of inventive step will neverthless be performed over all four documents.

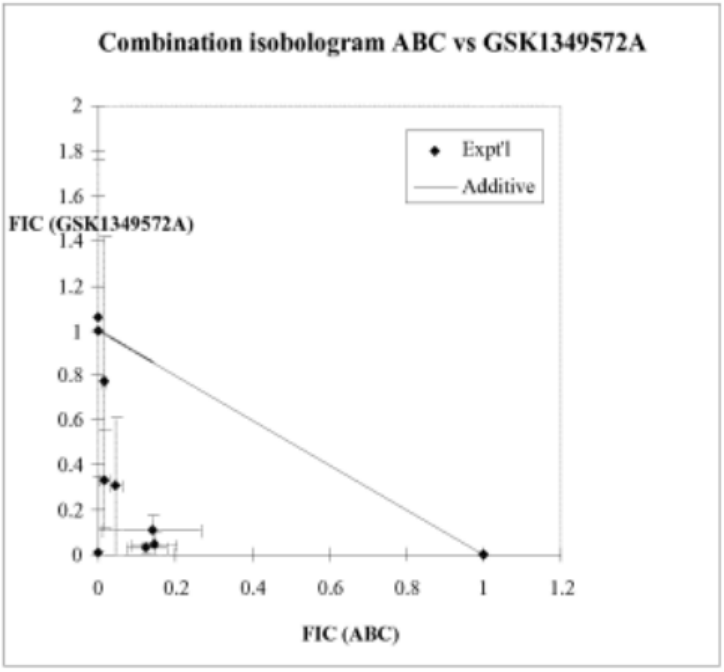
4.3 D11 as closest state of the art

4.3.1 The opposition division considered that the problem to be solved over D11 was the provision of an alternative synergistic combination of abacavir with an integrase inhibitor. Similar definitions were proposed by appellants 03 and 04 whereas appellants 01 and 02 defined the problem over D11 as the provision of an alternative combination.

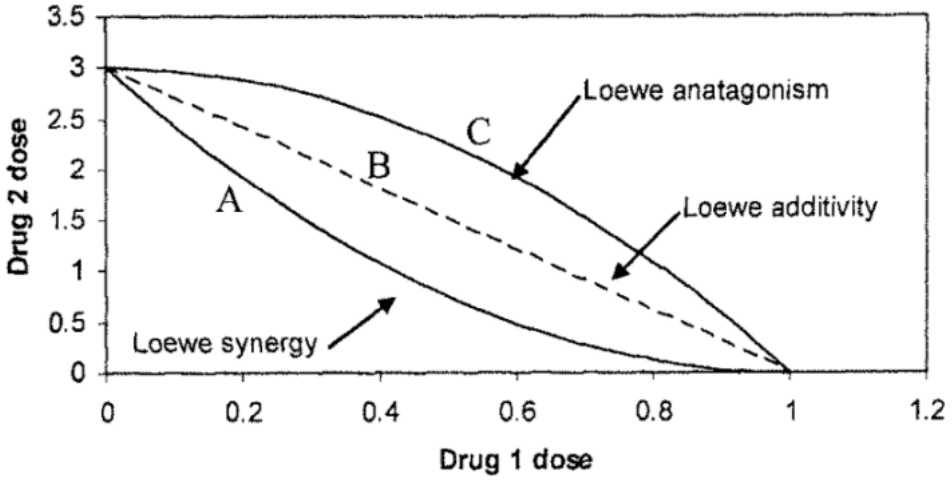
During the oral proceedings, the respondent defined the problem over D11 as the provision of an alternative synergistic combination having an improved activity or potency on the integrase enzyme.

4.3.2 The patent presents in Figure 1 an isobologram showing the effect of the claimed combination of abacavir and dolutegravir (see also par. [0077] and [0082] of the specification). The data points fall under the diagonal line which indicates the existence of a strong synergistic action between the two drugs, as shown below:

Figure 1: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with abacavir (ABC).



According to D57, synergy is indeed expressed when the points fall under the diagonal line as shown below by the line A, in contrast to line B which expresses the additivity of the drug effect and line C which expresses a drug antagonism (see pages 129-130 of D57):



The relevance of Figure 1 as evidence for a synergistic effect was initially objected to by the appellants, since it would not allow to draw any conclusions regarding an actual synergistic effect of the claimed combination in humans, and also in view of the low number of points tested and the absence of any points for abacavir between 0.5 and 1.0 on the abscissa.

In this regard the Board observes that isobolograms represent a standard and well recognised method for determining the presence of synergy between two drugs (see for instance D57). Moreover, paragraph [0077] of the patent explains how the isobologram of Figure 1 and of the patent was generated and there is no reason to consider that a similar synergistic interaction between the two drugs will not occur *in vivo*. There is furthermore no reason to doubt that the synergistic effect is present at lower as well as at higher concentrations of abacavir, since Figure 1 shows credibly that the two drugs have an overall synergistic activity rather than an additive activity. During the oral proceedings the appellants eventually acknowledged that Figure 1 of the patent was evidence of a synergistic effect of compound (I) with abacavir.

Hence, a synergic effect has been credibly shown for the combination of dolutegravir and abcavir, but it is not possible to conclude that a better or improved synergistic effect has been demonstrated over the combination disclosed in D11.

4.3.3 With regard to the improved activity or potency on the integrase enzyme alleged by the respondent, the Board considers that this technical effect is based on data relating to the use of dolutegravir as monotherapy whereas the invention disclosed in the original application and claimed in the granted patent relates to a combination of compounds. Thus, this effect is not relevant to the double combination claimed. Moreover, it is also not encompassed by the teaching of the application as filed in the sense of G 2/21.

It follows that the improved potency on the integrase enzyme cannot be taken into account in the definition of the technical problem.

4.3.4 The problem is therefore the provision of an alternative synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV. In view of Figure 1, it appears that this problem has been credibly solved.

4.3.5 With regard to obviousness, it must be determined whether it is obvious to replace the compound of example 19 of D11 in its synergistic combination with abacavir by dolutegravir to obtain an alternative synergistic anti-HIV combination.

In this context, documents D11, D14, D15, D17, D40, and D61 were cited and discussed.

(a) D11 shows in columns 75-76 and Table 4 two-drug combinations of the compound of example 19 with eight different nucleoside reverse transcriptase inhibitors, at a range of concentrations near the EC50 value of each compound. Table 4 shows that four nucleoside RT inhibitors (didanosine, stavudine, abacavir and emtricitibine) show synergistic antiviral effects in combination with example 19 at all effective levels and all molar ratios. For the other four RT inhibitors (zidovudine, lamivudine, tenofovir and zalcitabine) the overall effects of the combinations with example 19 are classified as synergistic to additive.

(b) Document D17 relates to polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase. It discloses dolutegravir in example Y-3 on page 116 or in dependent claim 32, among numerous other possible compounds. D17 recommends the combination of a compound as disclosed therein with another anti HIV compound having a different mechanism of action such as a reverse transcriptase inhibitor and/or a protease inhibiting agent but does not disclose any specific combination (see D17, page 78, lines 5 to 10).

(c) JP4295353B2 (D40) is the patent granted on the Japanese national phase application derived from D17. D40 discloses explicitly in claims 34-36 the compounds of formula (I), (II) and (III) of the contested patent and dolutegravir is the subject of claim 36.

(d) D14 reports in Table 3 how the compound GSK364735 interacts with known anti-HIV drugs. Of the nineteen compounds tested, nine were synergistic with GSK364735, *inter alia* with abacavir.

(e) D15 states on page 12 that "additive to synergistic antiretroviral activity was observed" when raltegravir was combined with each of several known anti-HIV drugs, including abacavir. This document does however not provide any further detail regarding the specific drugs with which raltegravir was synergistic and with which it was merely additive. It is also unclear from the document how many drugs interacted synergistically with raltegravir.

(f) D61 is an extract from the EMA's scientific discussion document concerning raltegravir. This document evaluates the antiviral activity of raltegravir with 18 licensed antiviral agents from all 4 classes (protease inhibitors, nucleoside/ nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and entry inhibitor; cf. page 6 of D61). The results show that when both tested compounds were present at lower concentrations, the effect of adding raltegravir to the other drug was null or additive. At higher compound concentrations, typically in excess of their IC50 values, raltegravir displayed synergistic activity with all other antiviral compounds tested.

Having regard to this state of the art, the Board is of the view that the skilled person, starting from the disclosed combination in D11 of the compound of example 19 as a HIV integrase inhibitor with abacavir as

reverse transcriptase inhibitor, would not have expected that the replacement of the compound of example 19 by dolutegravir provided a synergistic effect. In the Board's view, it is not correct to assert that a skilled person would simply assume that any new antiretroviral drug such as dolutegravir would even be compatible with, let alone synergistic with a known anti-HIV drug, since it is even not possible to exclude a possible drug antagonism. The reasons are the following:

- first, none of the documents suggests explicitly a combination of dolutegravir with abacavir. D11 exemplifies a high number of integrase inhibitors, i.e. over 280, and identifies as only integrase inhibitor to be synergistic with abacavir the compound of example 19. Moreover, D11 mentions a clear synergistic effect with only four reverse transcriptase compounds among the eight tested compounds, **which indicates that a synergistic effect is neither automatic nor predictable within the same pharmacological class of compounds.**
- the data provided in D14 confirms the conclusion that **synergy is not predictable**. Table 3 on page 906 provides data on the interaction of compound GSK364735 with known anti-HIV drugs. The table shows that of the nineteen compounds tested, only nine were synergistic with GSK364735, the remaining providing an additive effect, and no strong correlation between drug mechanism and synergy was observed, since not all combinations with a revertase transcriptase show a synergistic effect. The authors of D14 also underline on page 905 that it is critical, prior to initiating combination studies in clinical trials, to demonstrate that a particular combination has no or low potential for being antagonistic, at least at the level of antiviral activity;

- D17 and D40 are the only cited documents that have singled out dolutegravir among other possible integrase inhibitors, but these documents do not disclose any therapeutic combination and suggest a possible combination with either a reverse transcriptase inhibitor and/or a protease inhibitor without any indication of preference and with no further specification. In view of D17, the skilled person has still the choice between several possible types of combination without expectation of a synergistic effect;
- With regard to D15, the absence of any indication as to which combination of drugs with raltregravir has a synergistic effect makes the teaching of this document irrelevant. The same conclusion applies to the teaching of D61.

Consequently, the Board considers that none of the cited documents provides evidence or even a suggestion that the claimed combination might provide a synergistic anti-HIV action.

4.3.6 The argument of the appellants that D11, D14 and D15 each provides, at least, a reasonable expectation that a combination of abacavir and any integrase inhibitor is **always** synergistic also fails. These documents provide indeed the results for some integrase inhibitors, and according to the appellants the skilled person would have a reasonable expectation that these results would also apply to dolutegravir.

The Board disagrees with this position and notes that only D11 and D14 disclose specific synergistic combinations with abacavir, and that it does not appear possible to draw a general conclusion or a general technical concept from such limited disclosure.

It is also not credible that abacavir would provide a systematic synergistic effect with any integrase inhibitor, in the absence of any evidence. Having regard to the documents on file, the skilled person would not have had any reasonable expectation that a drug that is found to be synergistic with one integrase inhibitor would show a similar synergistic interaction with another integrase inhibitor. For example, as argued by the respondent (see point 9.27 of its reply), there are seven drugs that are synergistic both with the compound of formula (I) of the present patent (dolutegarvir) and with the compound of Example 19 of D11 (see results for stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir and enfuvirtide). Each of these seven compounds were also tested for synergy with the compound GSK364735 of D14, and only three of them were synergistic with GSK364735. The other four compounds, which did not interact synergistically with GSK364735, belong to three different mechanistic categories, including the nucleoside reverse transcriptase inhibitor (NRTI) category.

4.3.7 Consequently, the replacement of the compound of example 19 of D11 by dolutegarvir is not obvious and the subject-matter of claim 1 of the main request is inventive over D11 (Article 56 EPC).

4.4 D14 as closest prior art

4.4.1 The opposition division considered that the problem to be solved over D14 was the provision of an alternative synergistic combination of abacavir with an integrase inhibitor.

In the written proceedings, appellant 01 defined the problem over D14 as the provision of an alternative combination, while appellants 02 and 03 defined it as the provision of an alternative synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV.

In its letter dated 16 October 2023 the respondent argued that the drug combination defined in claim 1 represented an improved synergistic combination for treating HIV compared to the combination disclosed in D14. The respondent referred also to a number of additional technical effects which are however not relevant to the outcome of the present decision.

4.4.2 Figure 1 of the contested patent shows credibly a synergistic effect. Said synergic effect also appears to be **stronger** than the synergic effect shown by the combination disclosed in D14, **since the points shown in the isobologramm are located closer to the abscissa in Figure 1** (see point 4.3.2 above and Figure 5 of D14 on page 907).

4.4.3 The problem over D14 is therefore the provision of an improved synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV.

4.4.4 The claimed solution is not obvious for the same reasons as discussed previously over D11.

The conclusions would have been the same if the problem had been the provision of an alternative synergistic combination for treating HIV, instead of an improved synergistic combination, with the same arguments as when starting from D11 as closest state of the art.

4.5 D15 or D36 as closest prior art

4.5.1 The opposition division considered that the problem to be solved over D15 was the provision of an alternative synergistic combination of abacavir with an integrase inhibitor, and over D36 the provision of a combination of abacavir with an integrase inhibitor having a synergistic effect.

In the written proceedings, the problem was defined as follows by the parties:
- appellant 02 defined the problem over D15 as the provision of an alternative synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV, and over D36 as the provision of a synergistic combination of abacavir with an INSTI (HIV integrase inhibitor);
- appellant 03 defined the problem over D15 or D36 as the provision of an alternative synergistic combination of abacavir with an integrase inhibitor for the treatment of HIV;
- appellant 04 defined on page 7 of its statement of grounds of appeal the problem as the selection of an alternative integrase inhibitor for the Kivexa® OBT (lamivudine);
- the respondent defined the problem when D15 or D36 is taken as the closest prior art document as the provision of a new drug combination with synergistic activity.

4.5.2 The Board agrees with the definition of the problem as given by the respondent. Since the claimed combination shows a synergistic effect, while the compositions disclosed in D15 or D36 do not specify or prove any synergistic effect linked with the combination therapies disclosed therein, the problem can indeed

only be the provision of a synergistic combination for treating HIV.

Appellant 04 observed that synergy of the claimed combination was not proven in clinical trials and that no improvement was shown over the disclosure of D36. The Board does not see any reason to question in vitro tests for showing a synergistic anti-HIV effect, based on drugs which were already known and used for this therapeutic application. Such tests and isobologramm appear to be the usual way to prove a synergistic effect (see point 4.3.2 above). The presence of synergism indicates that the drugs work together to produce an effect greater than the sum of their individual effects. In the Board's view this is a valuable property of the drug combination which needs to be considered in the assessment of inventive step. There is no requirement to demonstrate a pharmacological effect through clinical data.

Consequently, the claimed solution is inventive since none of the cited documents provides an incentive to combine dolutegravir with abacavir in order **to obtain a synergistic anti-HIV effect** (see also point 4.3 above).

4.6 Consequently, the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated