Annex 1 – Facts and Arguments

Opposition Against European Patent EP2531027 B

Patentee: VIIV Healthcare Company

Opponent: Page White & Farrer Limited

1. Introduction

The above-identified European Patent (herein "the Patent") in the name of VIIV Healthcare Company (herein "the Patentee") is hereby opposed by Page White & Farrer Limited (herein "the Opponent") under Article 99 EPC.

The EPO is hereby instructed to debit the opposition fee directly from our deposit account, 2805.0076

1.1 Summary of Grounds for Opposition

The Patent is opposed under Article 100(a) EPC (lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), Article 100(b) EPC (insufficient disclosure (Article 83 EPC)) and Article 100(c) EPC (added subject matter (Article 123 EPC)).

1.2 Requests

It is requested that the Patent be revoked in its entirety. The opposition is made to the extent of all claims. Oral proceedings are requested should the Opposition Division be minded to grant anything other than the Opponent's request for revocation *in toto*.

1.3 Documents

The documents relied upon are:

P1 US 61/298,589 (priority document);

D1: ClinicalTrials.gov document ING112276; A Dose Ranging Trial of GSK1349572 and 2 NRTI in HIV-1 Infected, Therapy Naïve Subjects; 20th August 2009;

D2: XVIII International AIDS Conference, July 18-23 2010 • Vienna, Austria, page 287, Abstract THLBB205;

D3: AIDS 2010, 18th International AIDS Conference (IAC); July 18-23 2010; Vienna, Austria; "A Pilot Study of Abacavir/Lamivudine and Raltegravir in Antiretroviral-Naïve HIV-1 Infected Subjects;

D4: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents; December 1, 2009; Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services.

D5: Journal of the International AIDS Society 2010, 13(Suppl 4):O50;

D6: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 19th-22nd 2009; Capetown, South Africa; "Potent Antiviral Activity of S/GSK1349572, A Next Generation Integrase Inhibitor (INI), in INI-Naïve HIV-1-Infected Patients: ING111521 Protocol";

D7: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2010, pages 254–258 Vol. 54, No. 1;

D8 : J. Antimicrob. Chemother. 2010; 65: 1100–1107;

D9 : Journal of the International AIDS Society 2010, 13 (Suppl 1):S3;

D10: J. Antimicrob. Chemother. 2010; 65: 218–223; Advance publication 16 December 2009;

D11: British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008; HIV Medicine (2008), 9, 563–608;

D12: EACS - 12th European AIDS Conference November 11-14, 2009; Cologne, Germany; "A Pilot Study of Abacavir/Lamivudine (ABC/3TC) and Raltegravir (RAL) in Antiretroviral Naive HIV-1 Infected Subjects";

D13: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 19th-22nd 2009; Capetown, South Africa; "Pharmacokinetics (PK) and Safety in Healthy Subjects of S/GSK1349572, a Next Generation, Once-Daily HIV Integrase Inhibitor (INI)";

D14: J. Antimicrob. Chemother. September 23, 2010, pages 1-4;

D15: Meds & You; New approaches to antiretroviral therapy: Looking back at a decade of progress; Dr. Marianne Harris; 2008;

D16: Eur. J. Med. Res. (2009) 14(Suppl. III): 1-3;

D17: EPZICOM Product Label – September 2008;

D18: Review; De Clercq, Il Farmaco 54 (1999) 26–45;

D19: Review; Chesney, AIDS Patient Care and STDs; April 2003 (Vol. 17, Issue. 4, pages 169-S177);

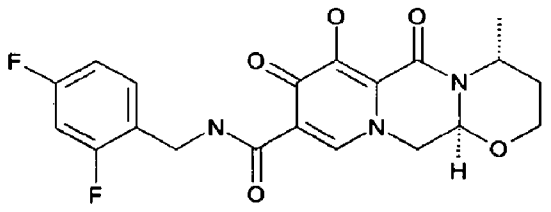
D20: Journal of Acquired Immune Deficiency Syndromes 2002; 31:S10-S15.

1.4 Technical Background

The present invention is concerned with combinations of known drugs used to treat HIV.

The Patent in suit sets out that due to their high potency and pharmacokinetic profile, certain HIV integrase inhibitors (INIs) are attractive as components in combination therapy.

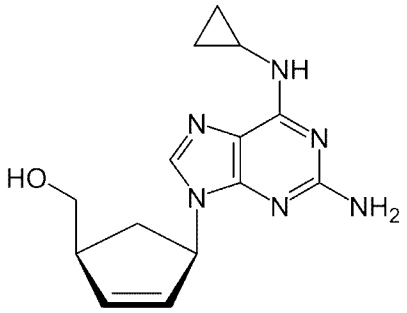
In particular, the claimed invention is concerned with combinations of known drugs containing an integrase inhibitor known as GSK1349572. The chemical name of GSK1349572 is (4R, 12aS)-N-[2,4-flurophenyl)methyl]-3,4,6,8,12,12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-2H-pyrido [1', 2':4,5]pyrazino [2,1 -b] [1 ,3] oxazine-9-carboxamide, and it also has the common name of Dolutegravir. It has the following structure:



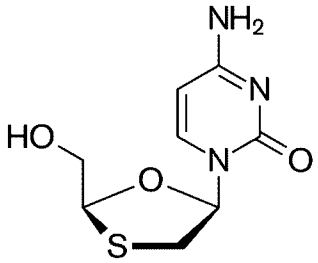
(I)

This compound is administered with other anti-retroviral compounds which are nucleoside reverse transcriptase inhibitors (NTRIs). Specifically, the NRTI's abacavir and lamivudine are claimed in combination with GSK1349572.

Abacavir is commonly shortened to ABC, has the formula {(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]cyclopent-2-en-1-yl}methanol,and the following structure:



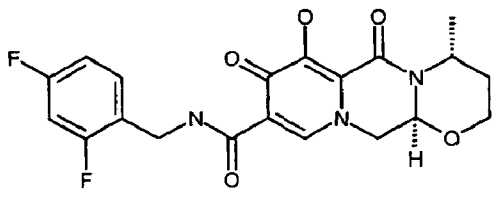
Lamivudine is the nucleoside analogue 2′,3′-dideoxy-3′-thiacytidine, commonly called 3TC. Its tradename is Epivir. It has the following structure:



1.5 Claimed Subject Matter and Interpretation

The Patent contains 9 claims, of which claim 1 is independent. Claim 1 as granted reads:

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



(I)

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

According to the patent in suit, paragraph [0027]:

> *Combination therapies comprise the administration of a compound of the present invention or a pharmaceutically acceptable salt thereof and another pharmaceutically active agent. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.*

Thus, the "combination" of claim 1 does not require a physical admixture of the active ingredients. They may be presented separately, i.e., in discrete dosage forms, as long as their administration complies with the requirements of sequentially or concurrency. This interpretation is supported by claims 7 and 8 which specify the simultaneous and sequential dosing. By virtue of the repercussive effect, claim 1 must be broader than this, and must be found to encompass separate dosing.

There is no data presented in the patent or the file history to support the claimed combination.

For example, paragraph [0087] only discloses that the combination of GSK1349572 and abacavir is synergistic. However, there is no mention of lamivudine. Furthermore, there is no disclosure as to what type of synergy is obtained between GSK1349572 and abacavir and no data to support such an allegation.

2. Lack of Priority

2.1 Claim 1

Granted claim 1 does not find basis in the priority application (P1).

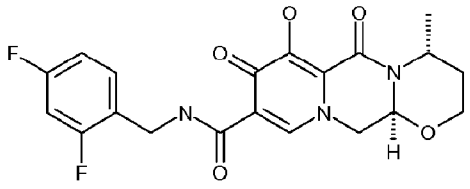
It is now generally accepted that priority entitlement must be assessed strictly. For example, under the EPC, Enlarged Board of Appeal Decision G2/98 held that:

> *... priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC 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 patent in suit claims priority from a US provisional application, USSN 61/298589 (P1).

Claims 1 and 2 of P1 disclose:

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



(I)

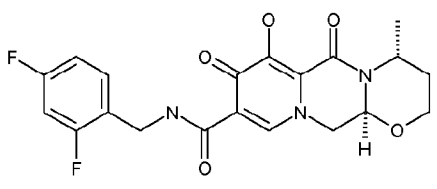
or a pharmaceutically acceptable salt thereof, with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir.

2. A combination according to claim 1 wherein the therapeutic agent is abacavir.

However, the combination with lamivudine is not mentioned anywhere in the claims of P1.

Lamivudine is mentioned on page 7, line 6 of P1, but this is in the context of an extensive list of therapeutic agents. P1, page 7, final paragraph discloses:

> The present invention features a combination comprising a compound of formula (I)



(I)

> or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from the group consisting of lamivudine, abacavir, tenofovir, efavirenz, GSK2248761, lersivirine, lopinavir, fosamprenavir, and atazanavir.

While this disclosure provides basis for a combination of GSK1349572 with more than one of the compounds specified, it does not provide direct an unambiguous disclosure of a combination of GSK1349572 or a pharmaceutically acceptable salt thereof, abacavir or a pharmaceutically acceptable salt thereof, and lamivudine.

Analogous disclosures to that in P1, page 7, final paragraph are found no page 8, second and fourth paragraphs, but do not provide the necessary basis for the combination claimed in the patent in suit.

Furthermore, the claimed combination is not supported by the priority document. There are no examples which specify the combination claimed in the patent in suit.

Accordingly, claim 1 of the patent in suit lacks a valid claim to priority. Hence, the effective priority date is the filing date of the patent in suit, namely 24th October 2011.

3. Added Matter (Article 100(c)/Article 123 EPC)

3.1 Claim 3

Granted claim 3 does not find basis in combination with the features of the claims on which it is dependent. Claim 3 requires that the pharmaceutically acceptable salt of abacavir is abacavir hemisulfate. This appears in the application as filed at page 9, lines 24-25. However, this disclosure is not in respect of any particular combination. As filed, the application related to compounds having the formulae (I), (II) and (III). The disclosure of abacavir hemisulfate is not in respect of any particular one of these. Nor is it disclosed in combination with lamivudine.

This has led to a new combination of previously undisclosed features, and therefore contravenes Article 123(2) EPC.

4. Lack of Novelty (Article 100(a)/Article 54 EPC)

4.1 D1 anticipates claims 1, 4-6 and 9

D1 is entitled "A Dose Ranging Trial of GSK1349572 and 2 NRTI in HIV-1 Infected, Therapy Naïve Subjects (ING112276)".

In the "Detailed Description" section on page 2 it states:

This Phase IIb study in HIV-infected antiretroviral naive adult subjects will include a dose-ranging evaluation of GSK1349572 10mg, 25mg and 50mg once daily blinded doses and a control arm of open label efavirenz 600mg once daily. Background ART for all study subjects will be chosen by the investigators and will be either Truvada or Epzicom/Kivexa. Data from the three doses of GSK1349572 will be compared on the basis of antiviral activity, safety/tolerability and pharmacokinetics over 16-24 weeks. Several planned interim analyses will evaluate data in real time; any doses considered inferior will be dropped and subjects on those doses of GSK1349572 will have the option to switch to either the highest dose still under investigation or the selected dose. Subjects will be able to remain in the study, unless they reach a stopping criterion, for at least 96 weeks.

Epzicom and Kivexa are alternative tradenames for fixed dose combination of abacavir sulphate and lamivudine (see D11, section 4.7.2 and D17, whole document).

This clearly discloses the combination of GSK1349572 with a combination abacavir and lamivudine. Accordingly, claim 1 lacks novelty.

D1 represents a Phase IIb clinical trial in HIV infected patients. Hence, claims 4, 5 and 9 also lack novelty.

Finally, Epzicom/Kivexa is a preforulated fixed dose composition which contains pharmaceutical carriers (D17, page 2, third paragraph). Hence, claim 6 lacks novelty.

4.2 D2 anticipates claims 1, 4, 5 and 9

D2 is entitled "Once-daily S/GSK1349572 as part of combination therapy in antiretroviral naïve adults: rapid and potent antiviral responses in the interim 16-week analysis from SPRING-1 (ING112276)."

The clinical trial (ING112276 is the same one referred to in D1. The abstract reports that:

S/GSK1349572, a next-generation HIV-1 integrase inhibitor, demonstrated potent antiviral activity in Phase2a with once-daily, unboosted dosing. Methods: SPRING-1 is a Phase 2b, multicentre, partially-blinded dose-ranging study in therapy-naïve adults, randomized 1:1:1:1 to 10mg, 25mg or 50mg of S/GSK1349572 or efavirenz (EFV) 600mg once-daily with either coformulated TDF/FTC or ABC/3TC.

Thus, the disclosure of D2 is essentially the same as D1. Accordingly, claims 1, 4, 5 and 9 lack novelty over D2.

4.3 D5 and D6 anticipate claims 1, 4-6 and 9

Analogous disclosures are also found in D5 and D6 which anticipate claims 1, 4, 5 and 9.

All of D2, D5 and D6 were published during the priority year. However, due to the lack of valid priority claim, they all represent Article 54(2) EPC prior art.

5. Lack of Inventive Step (Article 100(a)/Article 52/Article 56 EPC)

Should D1 not be considered to constitute a novelty destroying disclosure, neither claim 1 or any of the dependent claims can be considered to involve an inventive step in light thereof or in light of other prior art. The reasons for this are outlined below.

Before addressing the specifics of the problem and solution approach in respect of the present claims, the Opponent wishes to identify aspects in this field of technology which are considered to represent the common general knowledge.

5.1 Common General Knowledge

5.1.1 What was the Standard of Care at the Priority Date?

At the priority date it was well known that it was conventional to use double and preferably triple combinations of anti-HIV drugs to treat HIV infection. For example, the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents in the USA (D4, page 37 states:

Panel's Recommendations:

- ***The Panel recommends initiating antiretroviral therapy in treatment naïve patients with 1 of the following 3 types of regimen:***
  - ***NNRTI + 2 NRTI***
  - ***PI (preferably boosted with ritonavir) + 2 NRTI***
  - ***INSTI + 2 NRTI***
- ***The Panel recommends the following as preferred regimens for treatment naïve patients:***
  - ***Efavirenz + tenofovir + emtricitabine (AI)***
  - ***Ritonavir-boosted atazanavir + tenofovir + emtricitabine (AI)***
  - ***Ritonavir-boosted darunavir + tenofovir + emtricitabine (AI)***
  - ***Raltegravir + tenofovir + emtricitabine (AI)***
- ***A list of Panel recommended alternative and acceptable regimens can be found in Table 5a.***
- ***Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.***
- ***Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.***

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor

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.

In this regard, INSTI is an integrase strand transfer inhibitor. This is the family of antiretroviral drugs which GSK1349572 of the present invention is a member of. While GSK1349572 is not mentioned in D4 (as it was still in the early experimental phase at the publication date of D4), D4 clearly teaches that the recommended treatment regime is a combination of INSTI and two NRTIs.

According to the British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (D11), the recommended choice of NRTI combinations is referred to on page 576, section 4.9:

In light of the findings of ACTG 5142, the recommendation of the Writing Group is for use of an efavirenz-based regimen for initial therapy, reserving boosted PIs for later. This is based on the efficacy data, the low risk of toxicity, the ease of administration, and the genetic frailty of an NNRTI in patients failing a boosted PI regimen. However, less class-emergent resistance is observed with boosted PIs, underscoring the importance of individualizing therapy. It is also recommended that Truvada and Kivexa are the nucleoside backbones of choice.

In respect of integrase inhibitors, D11, page 583, section 7.3 states:

Integrase inhibitors target the viral integrase enzyme, which plays an important role in the viral life cycle. The integrase inhibitors that are the furthest in clinical trial development are raltegravir (formerly MK-0518) and elvitegravir (formerly GS9137). Currently, phase III trials of raltegravir in treatment naı¨ve and treatment-experienced patients are ongoing and it has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for use in treatment-experienced patients. Elvitegravir is going into phase III development for treatment-experienced patients. It is metabolized by CYP3A4 and, in studies carried out to date, it has been administered with ritonavir, allowing once-daily dosing; raltegravir is given twice daily.

Thus, at the priority date, there was a clear recommendation from various national guidelines that anti-retroviral drug combinations ("cocktails") were the recommended HIV treatment. The only two NRTI "backbone" combination treatments recommended were Truvada and Kivexa, the latter being the trade name of a combination of abacavir and lamivudine. Furthermore, a combination of integrase inhibitor with a double NRTI drug combination was also recommended.

Conclusions: A triple drug administration regimen including a double NRTI "backbone" was conventional and recommended as the priority date.

5.1.2 Commercially Available Integrase Inhibitors (INSTIs)

At the priority date, the use of integrase inhibitors was a relatively new phenomenon. As pointed out above, they had found their way onto the various national Guidelines for HIV

treatment. However, only raltegravir (formerly MK-0518) and elvitegravir (formerly GS9137) were licensed at the priority date. It is important to understand what was common general knowledge about these promising drugs from a new class of anti-HIV agents.

D4, page 46, second paragraph states:

> *INSTI-BASED REGIMEN (INSTI + 2 NRTIs)*
>
> *Raltegravir is an INSTI that was first approved for use in combination antiretroviral regimens for treatment-experienced patients with HIV strains resistant to multiple antiretroviral drugs. It is now approved by the FDA for use in treatment-naïve patients, based on results of STARTMRK, a Phase III study that compared raltegravir (400mg twice daily) to efavirenz (600mg once daily), each in combination with tenofovir/emtricitabine, in treatment-naïve subjects.*
>
> ...
>
> *Comparisons of raltegravir-based regimens with other regimens in treatment-naïve subjects have not yet been reported, and there is less experience with raltegravir than with efavirenz or boosted PIs for initial therapy. In addition, raltegravir has to be administered twice daily, a potential disadvantage when compared with some other regimens. Raltegravir, like efavirenz, has a lower genetic barrier to resistance than ritonavir-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial. Its use with other dual NRTIs (such as abacavir/lamivudine or zidovudine/lamivudine) may be acceptable, but more definitive data for these regimens are needed (CIII).*

In respect of integrase inhibitors, D11, page 583, section 7.3 states:

> *Currently, phase III trials of raltegravir in treatment naı̈ve and treatment-experienced patients are ongoing and it has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for use in treatment-experienced patients. Elvitegravir is going into phase III development for treatment-experienced patients. It is metabolized by CYP3A4 and, in studies carried out to date, it has been administered with ritonavir, allowing once-daily dosing; raltegravir is given twice daily.*

Thus, raltegravir was clearly seen as a promising weapon in the armoury against HIV infection. However, it's twice daily administration was clearly viewed as a disadvantage. This observation is further supported by the table on page 52 of D4, INSTI row, "disadvantages" section). Furthermore, it was conventional to administer it with dual NRTIs (such as abacavir/lamivudine).

Conclusions: Integrase inhibitors were a relatively new but highly promising drug class for fighting HIV infection. Raltegravir was the first integrase inhibitor to be approved for the market, but had the drawback of requiring twice daily administration.

5.1.3 Once-Daily Dosing and Treatment Adherence

Due the importance of adherence to drug administration regimes, at the priority date there was (and had been for some time) a significant move towards simplifying the administration regimes in order to improve compliance. The main way of achieving this was to reduce the number of times the drugs had to be administered. Therefore, there was a clear move towards once-daily administration.

The authors of D18 are referred to on page 38, right column, and summarised in table 3 as follows:

> *In view of all these considerations, and the remarks made above on the optimization of drug treatment regimens, a few recommendations could be formulated so as to ensure a successful treatment of HIV infections. These recommendations (Table 3) concern NNRTIs as well as any other anti-HIV drugs.*

Table 3
Recommendations for clinical use of anti-HIV drugs, including NNRTIs

1.	Use different compounds in multiple (double, triple, quadruple, ...) drug combinations.
2.	At sufficiently high (but subtoxic) doses.
3.	Starting as soon as possible after the HIV infection.
4.	With the aim to achieve complete suppression of virus replication (plasma viral load below detection limit).
5.	And to prevent the development of virus drug resistance.
6	Ensuring full compliance (patient taking his/her medicine).
7.	While improving on the convenience of drug dosing (preferably once daily).
8.	Minimizing adverse side effects of the drug.
9.	Continuing drug treatment as long as required for a sustained suppression (and, ideally, eradication of the virus from the organs and from the organism).
10.	Making the anti-HIV drugs widely available (at affordable costs).

Thus, the recommendations based on a comprehensive literature review concluded that, *inter alia*, multiple drug combinations should be used and once daily dosing was preferred in order to improve patient compliance.

D18 mentions HAART administration regimes. This is the acronym for Highly Active Antiretroviral Therapy, and a review of adherence to HAART regimes is provided in D19. On page 169, right column, this document states:

> *In contrast to most chronic conditions, successful treatment of HIV infection requires that adherence be nearly perfect in order to reduce viral loads and prevent the emergence of drug resistant variants, which reduce future treatment options and can be fatal.*

Clearly then, rigid adherence to the drug administration regime was thought to be paramount at the priority date of the patent in suit. D19, page 172, left column cites dosing schedules have a pervasive influence on adherence:

> *As in other chronic diseases, once- or twice-daily dosing is preferred.*[46] *One study showed that twice-daily dosing or less leads to better overall adherence (at least 80%) to anti-HIV medication compared with more frequent dosing.*[46] *Twice-daily dosing is associated with better adherence than three-times-a-day dosing.*[37,47]

And page 172, right column, line 6 continues:

> *Once-daily formulations of existing drugs, and new drugs in development, are being investigated. Several studies involving regimens with once-daily dosing of both current and investigational agents have yielded promising results, in comparison with current regimens that involve dosing two or three times daily.*[49,50]

It also appears that once-daily HAART treatment was considered the standard of care at the priority date. For example, D20 is entitled "Once-Daily HAART: Toward a New Treatment Paradigm", and presents a rationale and clinical support for the use of once-daily treatments of anti-viral drug combinations. The abstract sets out:

> *Highly active antiretroviral therapy (HAART) suppresses HIV replication to undetectable levels with concomitant increases in CD4+ T-cell counts and improvement in immune function. However, complex dosing, large pill burdens, and side effects make long-term adherence difficult, with the result that patients may achieve only suboptimal exposure to antiretroviral drugs, increasing the risk of treatment failure and viral resistance. Treatment strategies in other chronic conditions show that simpler regimens with fewer daily doses and fewer pills per dose increase adherence and treatment success. This article discusses adherence and its influence on treatment outcomes, reviewing evidence from recent studies that have evaluated the safety and efficacy of treatment regimens with reduced pill burdens and improved tolerability.*

The conclusions section (S14, right column) summarises:

> *Adherence remains one of the greatest challenges for patients receiving antiretroviral treatment. Increased simplification of treatment regimens should assist in improving the long-term adherence to therapy and maintaining treatment efficacy. In the future, once-daily regimens will become the standard of care for HIV infection. At present, several currently available antiretroviral drugs can be used once daily or have the pharmacokinetic potential for once-daily dosing, and others are in development.*

Conclusions: Once-daily dosing of anti-retrovirals was conventional and recommended by the various national Guidelines in order to improve adherence. It was recognised that compatible pharmacokinetic profiles of drug combinations that justify once-daily use should be used.

5.2 Problem & Solution Approach

As set out above, D1 is considered to anticipate a number of the granted claims as there is a clear disclosure of GSK1349572 being used to treat HIV in combination with abacavir/lamivudine.

For those claims that are arguably novel, such as claims 7 and 8, the manner of administration ("simultaneous" or "sequential") does not add anything over D1. Therefore, these claims are self-evidently obvious in light of D1 alone, or in combination with the common general knowledge.

If the claims are found novel, none of the claims are considered inventive in light of D1. However, *arguendo,* apart from D1 being considered the closest prior art, a number of other documents could be considered the closest prior art.

5.2.1 D2 as the Closest Prior Art

D2 is a conference report from shortly before the priority date. It discloses the resistance profile of GSK1349572. In the author conclusions section on page 1, it is stated that GSK1349572 "exhibited in vitro activity against most clinical isolates obtained from patients failing RAL-based therapy." RAL-based therapy is a reference to raltegravir.

Notwithstanding the lack of novelty arguments, if D2 is considered not to disclose the combination of GSK1349572 with abacavir/lamivudine, then the problem to be solved in light of D2 is the provision of an effective anti-HIV drug combination.

As pointed out in sections 5.1.1-5.1.3 above, combinations including an intergrase inhibitor with a double NRTI backbone was the recommended drug regimen at the priority date. At the priority date, the only duel NRTI drug combinations recommended were abacavir/lamivudine or zidovudine/lamivudine. As the specific NRTI backbone of abacavir/lamivudine are disclosed in D2, it was obvious to combine GSK1349572 with abacavir/lamivudine.

5.2.2 D12 as the Closest Prior Art

Alternatively, the skilled person may start from D12.

D12 presents a pilot study of an abacavir/lamivudine in combination with raltegravir in HIV infected subjects.

D12 fails to disclose GSK1349572. Thus, the problem to be solved is the provision of an alternative anti-HIV treatment.

D6 would be combined with the teaching of D12 as D6 discloses a "next generation intergrase inhibitor" which is GSK1349572. The summary section of D6 states that this compound has "unprecedented antiviral activity" and has no raltegravir resistance substitutions. Furthermore, GSK1349752 is stated to be the "only once-daily, unboosted INI [intergrase inhibitor] in clinical development".

Thus, the skilled person would obviously replace raltegravir from the combination disclosed in D12 for a number of reasons: (1) simply because GSK1349572 is a better drug; (2) the resistance profile of GSK1349572 is complementary to that of raltegravir. Thus, in a failing therapy (due to acquired resistance) in D12, GSK1349572 provides an obvious replacement for raltegravir.

Analogously, D12 would be combined with D7. D7 represents a similar disclosure to D6. In this regard, GSK139572 is described as an investigational HIV intergrase inhibitor which is designed to retain activity against raltegravir and elvitegravir-resistant HIV (page 254, left column, second paragraph).

Furthermore, GSK1349572 is said to have a pharmacokinetic profile that suggests once daily administration (see abstract). Thus, not only is GSK1349572 an obvious replacement for drug regimens that contain raltegravir from a resistance point of view, but it also overcomes the well-known shortcoming of raltegravir; namely the need for twice-daily administration. This is particularly significant shortcoming in terms of medication adherence. Furthermore, the skilled person would know that duel NRTI regimens such as abacavir/lamivudine (kivexa) were conventionally administered (and in deed designed to be) once-daily. Hence, GSK1349572 is an obvious replacement for raltegravir from a pharmacokinetic perspective.

Similar comments apply in respect of the combination of D12 with D8.

D8, page 1103, right column, line 8-20 discloses that:

> *The most recent intergrase inhibitor to enter clinical development (S/GSK1349572) has generated enthusiasm based on pre-clinical and early clinical studies. ... in contrast to raltegravir, S/GSK1349572 has limited inter-subjects pharmacokinetic variability. Preliminary date also suggests that this drug has a higher barrier to resistance in vitro than raltegravir or elvitegravir and appears to retain activity in vitro against many raltegravir resistant variants.*

Thus, based on D8, GSK1349572 is an obvious replacement for raltegravir.

Similarly, a combination of D12 with D10 renders the claims obvious.

D10, page 218, right column, second paragraph discusses the failure of raltegravir due to the development of mutations. This is contrasted with GSK1349572 which is said to be active against raltegravir and elvitegravir resistant mutations.

Furthermore, D10, page 222, left column, first paragraph refers to the limitations of raltegravir due to its less convenient, twice-daily dosing. This section goes on to refer to the "most prescribed nucleoside analogue backbones (eg. Truvada and Kivexa) as these are given once daily.

This paragraph finishes with the comments:

> *Hopefully the new second-generase integrase inhibitors under development will keep the advantages of raltegravir but overcome some of its limitations, as they will be administered once-daily and display a higher genetic barrier to resistance.*

Thus, there is a clear link between the once-daily administered second-generation integrase inhibitors such as GSK1349572 and the most prescribed, once-daily nucleoside analogue 'backbones' such as Kivexa (abacavir/limovudine).

5.3 Dependent Claims

None of the dependent claims involve an inventive step for analogous reasons to claim 1.

5.4 Other documents of interest

D9 is relevant to the inventive step of the present claims for analogous reasons to to the previous documents. In particular, the final paragraph on page 5 reads:

> *The 10-day monotherapy study of the potent investigational integrase inhibitor, S/GSK1349572, demonstrates the value of continued antiretroviral development [12]. The past few years witnessed the arrival of several strong and tolerable antiretrovirals in new and existing classes. There is no reason to assume that even better drugs cannot be developed.*

Likewise, D13 discloses that GSK1349572 has a favourable pharmacokinetic profile for once-daily dosing, and potent activity.

D14, page 3, right column, final paragraph discloses:

> *S/GSK1349572 has a long half-life that allows once-daily dosing (without pharmacological boosting), and importantly appears to be active in vitro against some raltegravir- and elvitegravir-resistant strains.*

Thus, raltegravir's replacement by GSK1349572 is obvious based on the clear advantage that GSK1349572 possesses.

D15, page 2, first and second paragraphs disclose:

> *Once Daily Dosing*
>
> *Another important discovery was that some NRTIs could be taken once a day without losing their effectiveness. NRTIs that were originally prescribed twice daily, and have been shown to work just as well taken once a day, include ddI, 3TC, and abacavir. The newest drugs in this class, tenofovir and FTC, are also used once daily. So now you can have a two-drug NRTI regimen, such as abacavir/3TC or tenofovir/FTC, that only needs to be taken once a day. Some NRTIs, such as AZT and d4T, still need to be taken twice a day.*
>
> *Fixed-dose combinations*

These formulations combine two or more antiretroviral (ARV) drugs in the same pill. The main advantage is that you have to take fewer pills to get the same amount of medication. For example, instead of taking one capsule of AZT and one tablet of 3TC twice a day, you can take one Combivir® pill twice a day, which contains the same total amount of AZT and 3TC. Kaletra® contains lopinavir and ritonavir, so you don't have to take ritonavir separately. The most commonly used NRTI fixed-dose combinations are Truvada® (tenofovir + FTC) and Kivexa® (abacavir + 3TC), which both provide a one-pill, once-a-day NRTI "backbone."

This disclosure would motivate the skilled person to combine Kivexa with a once-daily integrase inhibitor such as GSK1349572. This would meet the requirements of the guidelines, hence would constitute conventional therapy.

D16 discloses:

Resistance studies have described Q148R to be the prime mutation conferring resistance to both raltegravir and elvitegravir. More recently, other new compounds such as S/GSK1349572 have been presented which demonstrated activity in vitro against laboratory HIV strains that contain mutations associated with raltegravir and elvitegravir resistance (e.g., Q148R, N155H and Q148H/G140S). These data suggest that S/GSK1349572 has the potential to be used after a previous first generation integrase inhibitor failure.

The implication for replacing raltegravir with GSK1349572 are therefore obvious.

6. Insufficiency (Article 100(b)/Article 83 EPC)

6.1 Claim 2

The patent provides no disclosure as to how one might prepare the sodium salt of GSK1349572. Thus, claim 2 lacks compliance with Article 83 EPC.

On the other hand, if it is within the normal remit of the skilled person to prepare the sodium salt of GSK1349572, then claim 2 must be obvious.

7. Summary

The Patent lacks novelty, inventive step, contains an insufficient disclosure and does not comply with the requirements of Article 123(2) EPC. Accordingly, it should be revoked in its entirety.