IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX CORP.
Petitioner
v.
VIIV HEALTHCARE UK LTD.
Patent Owner

U.S. Patent No. 6,417,191 to Barry *et al*.
Issue Date: July 9, 2002
Title: Synergistic Combinations of Zidovudine, 1592U89 and 3TC

Inter Partes Review No. Unassigned

Petition for *Inter Partes* Review of U.S. Patent No. 6,417,191 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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I. INTRODUCTION

APOTEX CORP. petitions for *Inter Partes* Review, seeking cancellation of claims 1-51 of U.S. Patent No 6,417,191 to Barry and St. Clair ("the '191 patent") (APO1001), which is owned by VIIV HEALTHCARE UK LTD.

II. OVERVIEW

The challenged claims of the '191 patent recite obvious combinations of well-known anti-HIV (human immunodeficiency virus) drugs, methods of using such combinations, and patient packs comprising such drugs. More specifically, the claims recite various combinations of the drugs known as:

- (1S,4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene- 1-methanol, which is also known as "**1592U89"** or **"abacavir"**;
- 3'-azido-3'-deoxythymidine, which is also known as "**zidovudine"** or **"AZT"**; and
- (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2- one, which is also known as **"lamivudine"** or "**3TC**."

Abacavir, AZT, and 3TC are nucleoside analog reverse transcriptase inhibitors ("NRTIs"), and they function by inhibiting replication of the virus. APO1003; APO1006, ¶28; APO1010, 516:1:1; APO1011, 1:2; APO1014, 151:Abstract and

Table 1.

Each of these drugs was known in the prior art, and AZT and 3TC had previously been used in combination in a highly-effective composition and method for treating HIV. APO1006, ¶28; APO1010, 516:1:1; APO1011, 1:2; APO1012, 11:2:6; APO1013, 2:6-3:2; APO1014, 151:Abstract and Table 1. Similarly, abacavir was known to be a potent, selective anti-HIV drug, and it had been used in combination with AZT to synergistically inhibit HIV in *in vitro* studies of HIV infection. APO1003; APO1017. By the March 1995 alleged priority date, persons of ordinary skill in the art ("POSAs") understood that formulating and using anti-retroviral drugs in combination provided benefits over monotherapies for treating HIV infections. APO1004, 907:1:1-907:2:1 and 908:1:2; APO1006, ¶¶30-31, 43, 53, 76, 87, and 137. And POSAs recognized that three-drug combinations offered advantages over two-drug combinations, *e.g.*, to further delay the development of drug resistance and prolong efficacy against HIV. APO1004, 907:1:1-907:2:1 and 908:1:2; APO1006, ¶41. Indeed, the combination of AZT and 3TC was among the most effective anti-HIV treatments known as of March 1995. APO1011, 1:2 and 2:1; APO1012, 11:2:6; APO1013, 2:6-3:2. And abacavir had come to be recognized as an "attractive," "promising" potent and selective drug candidate for use in combination therapies, and it was used in combination with AZT to great effect. APO1003; APO1017. With this information in hand, a POSA would have

had a reason to formulate and use a three-drug regimen by combining abacavir with the highly effective combination of AZT and 3TC. APO1006, ¶¶48-53, 111-112, 116, and 145. And a POSA would have had a reasonable expectation of success with such a combination because AZT and 3TC were known to be highly effective, and abacavir also was known to have potent anti-HIV activity both alone and in combination with AZT. APO1006, ¶¶49, 54, 110-112, 117-118, and 145.

A POSA also would have had a reason to formulate and use 3TC and abacavir in combination, as claimed, because for certain patients, AZT needed to be withdrawn from the treatment regimen or be avoided in favor of other drugs. APO1004 1:2; APO1006 ¶¶44 and115-116. And a POSA would have had a reasonable expectation of success in formulating and using a combination of abacavir and 3TC, as claimed, because each drug was known to be very effective in inhibiting HIV replication while having very low toxicity. APO1002, 4:21-26; APO1003; APO1005, 2:2; APO1006 ¶¶36, 44, 51, 117.

Recognizing that AZT, 3TC, and abacavir were well-known and had been used in various combinations, the inventors of the ‘191 patent asserted that it was unexpected that an *in vitro* synergistic anti-HIV effect would be achieved by combining abacavir, AZT and 3TC. See, e.g., APO1033, 221-222:¶9; APO1033, Response to Office Action dated Sept. 14, 1999; APO1029, 37. But the claims do not require any synergistic effect. APO1001, claims. And it was not unexpected

that the combination of these three drugs provides an *in vitro* synergistic anti-HIV effect. APO1006, ¶¶121-134. Indeed, the combination of AZT and 3TC had already been shown to provide an *in vitro* synergistic anti-HIV effect, as had the combination of AZT and abacavir. APO1002, 4:20-26; APO1003; APO1011, 2:1; APO1012, 11:2:6; APO1013, 2:6-3:2. Compared to this prior art, the synergistic effect seen when combining AZT, 3TC, and abacavir was not at all unexpected to a POSA. APO1006, ¶¶121-134. Thus, the invention does not provide unexpectedly superior results as compared with the closest prior art. Petitioner is reasonably likely to prevail in showing unpatentability, and trial should be instituted.

III. STANDING (37 C.F.R. § 42.104(a)); PROCEDURAL STATEMENTS

Petitioner certifies that (1) the '191 patent is available for IPR and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '191 patent. This Petition is filed in accordance with 37 CFR § 42.106(a). A Power of Attorney and an Exhibit List are filed concurrently herewith. The required fee is paid online via credit card. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

Real Party-In-Interest (37 C.F.R. § 42.8(b)(1)) is: APOTEX CORP.

Related Matters (37 C.F.R. § 42.8(b)(2)): *ViiV Healthcare UK Ltd., et al. v. Lupin Ltd., et al.*, C.A. No. 11-576-RGA (D.Del.), not involving Petitioner.

Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel	Back-Up Counsel
Eldora L. Ellison (Reg. No. 39,967) STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C. 1100 New York Avenue, NW Washington, DC 20005 202.772.8508 (telephone) 202.371.2540 (facsimile) eellison-PTAB@skgf.com	Ralph W. Powers III (Reg. No. 63,504) STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C. 1100 New York Avenue, NW Washington, DC 20005 202.772.8876 (telephone) 202.371.2540 (facsimile) Tpowers-PTAB@skgf.com

Notice of Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence regarding this Petition to lead counsel at the above address.

Petitioner consents to service by email at: eellison-PTAB@skgf.com and tpowers-PTAB@skgf.com.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(A))

Petitioner requests IPR and cancellation of claims 1-51. Petitioner's full statement of the reasons for the relief requested is set forth in detail in § VIII.

VI. CLAIM CONSTRUCTION

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations in light of the specification of the '191 patent. Terms not explicitly discussed below are plain on their face and should be construed to have their ordinary and customary meanings.

The term "**physiologically functional derivative**" is explicitly defined in the patent as "any physiologically acceptable salt, ether, ester, salt of such ester of 1592U89, zidovudine or 3TC; or solvates of any thereof and their physiologically functional derivatives; or any other compound which upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof." APO1001, 2:32-39.

The term **"(1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol**" should be construed to encompass "1592U89" and "abacavir," as these names are used interchangeably in the patent or in the art. APO1001, 1:10-11; APO1007, 57:4; APO1006, ¶17.

The term "**(2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one**" should be construed to encompass "3TC," and "lamivudine," as these names are used interchangeably in the patent or in the art. APO1001, 1:12-14; APO1007, 33:1; APO1006, ¶19.

The term "**zidovudine**" should be construed to encompass "3'-azido-3'-deoxythymidine" and "AZT," as these names are used interchangeably in the patent or in the art. APO1001, 1:11-12; APO1007, 33:1; APO1006, ¶18.

Claim 31 recites a **"patient pack"** comprising **"at least one"** active ingredient selected from abacavir, AZT, and 3TC. Under the broadest reasonable

interpretation, only a single active ingredient (together with an information insert) needs to be provided in the patient pack.

Claims 1-15, 20-30, and 32-40 are directed to methods for the "**treatment or prevention**" of the symptoms or effects of an HIV infection in an infected animal. While not specifically defined in the '191 patent specification or its prosecution history, a POSA would interpret the phrase "treatment or prevention" in accordance with its plain and ordinary meaning. APO1006, ¶20. None of the '191 claims require any particular magnitude of effect or any particular level of efficacy. Similarly, the term "**therapeutically effective amount**" should be given its plain an ordinary meaning, and it does not require any particular level of therapeutic efficacy. *Id.*

Certain claims, e.g., claim 3, recite "**ratios … by weight**." That term should be construed to represent a range of possible weight relationships between the drugs recited in the claim. APO1006, ¶25. For example, a ratio of 1 to 1:1 would indicate that the three drugs were present at equal weights. *Id.* A ratio of 1 to 2:1 would indicate that the second drug was present in twice the amount by weight of the first and third drug, and so on. *Id.*

The remaining terms in claims 1-51 are plain on their face and should be construed to have their ordinary and customary meanings.

VII. PERSON OF ORDINARY SKILL IN THE ART AND STATE OF THE ART

A person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA in the art of methods and formulations for treating or preventing HIV infection would have had knowledge of the scientific literature concerning methods and formulations for treating HIV infection as of March 1995. Such a POSA would have had knowledge of strategies for inhibiting viral replication and for formulating anti-HIV therapeutics. Typically, a POSA would have had a medical degree or a Ph.D. in virology or in a related field in the biological, pharmaceutical, or chemical sciences, with experience in anti-viral therapies. A POSA would have known how to research the scientific literature regarding treatment of retroviral infections. Also, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others in the team, e.g., to solve a given problem. For example, a physician, a virologist and a pharmaceutical formulator may have been part of the team.

As of March 1995, the state of the art included the teachings provided by the references discussed in each of the unpatentability grounds set forth below. Additionally, a POSA would have been aware of other important references relating to HIV therapies.

HIV is a retrovirus (i.e., it has a genome made of RNA), and it can infect and kill immune cells of its host, leading to progressively fewer immune cells and causing acquired immunodeficiency syndrome (AIDS). In its normal life cycle, HIV's RNA genome is converted into DNA by the enzyme reverse transcriptase. The viral DNA then becomes inserted into the genome of the host cell, where it targets immune cells and can cause Acquired Immunodeficiency Syndrome (AIDS). APO 1006, ¶27.

By March 30, 1995, researchers had developed various drugs that could be used to treat HIV infections. *See, e.g.*, APO1006, ¶¶27-31; APO1008, 963:2:2; APO1009, Abstract. At that time, nucleoside reverse transcriptase inhibitors (NRTIs) were the principal—and the only FDA-approved—category of available antiviral agents. APO1006, ¶¶28-29; APO1008; APO1009. NRTIs compete with endogenous nucleosides for binding to a complex of HIV reverse transcriptase and the template RNA genome. APO1006, ¶28; APO1014, 152:1. Incorporation of a NRTI prematurely terminates reverse transcription of the viral RNA genome into DNA, interfering with the viral life cycle. APO1006, ¶28. For example, the NTRI known as AZT mimics endogenous thymine and was well known prior to March 1995 to be useful for treating HIV infections. APO1010, 516:1:1; APO1011, 1:2.

Prior to March 1995, POSAs knew that, over time, the HIV virus can mutate and become resistant to drugs. APO1004, 907:1:1; APO1006, ¶30. To slow the

development of resistance, clinicians began implementing combination drug therapies by March 1995. APO1004, 907:1:1; APO1006, ¶¶31-44**.** Such combinations could offer the advantages of synergistic interactions between drugs, being able to reduce toxicity by using lower doses, delaying the emergence of drug-resistant HIV, and potentially targeting different reservoirs of virus. APO1004, 907:1:2-907:2:1; APO1010, 516:1:1. Some combination therapies included multiple nucleoside NRTIs. *See, e.g.*, APO1004, 908:2:2; APO1010, 518:1:4-520:1:2. Such combinations target different nucleosides and thus don't compete for binding to the same populations of reverse transcriptase-template complexes. APO1006, ¶¶31, 124-125.

Other combination therapies being examined as of the alleged March 1995 priority date included NRTIs together with "non-nucleoside reverse transcriptase inhibitors" ("NNRTIs") or with "protease inhibitors" ("PIs"). *See, e.g*, APO1004, 902:2:1; APO1010, 520:2:3-521:1:3.

For example, AIDS Alert (APO1012), published January 13, 1995, disclosed the results of clinical trials comparing combination therapy versus monotherapy in HIV patients. *Id.* at 11:2:2; APO1006, ¶¶42-43. AIDS Alert taught that the combination of AZT and 3TC "may have a synergistic effect that may increase antiretroviral benefits even more than the other combinations." APO1012, 11:2:6. And it taught that "[p]articipants on [AZT-3TC] combination therapy had an

increase of 80 [CD4 immune] cells above baseline after 24 weeks, compared with seven cells below baseline for patients on monotherapy" APO1012, 12:1:2. And DeNoon (APO1013), published February 20, 1995, would have conveyed to a POSA that the combination of 3TC and AZT "has the most potent and longest lasting effect of any antiretroviral strategy yet tested in clinical trials" and that this combination "gives the greatest magnitude and longest lasting antiviral effect yet seen." *Id.* at 2:1 and 2:5. DeNoon also reported that "It's possible that 3TC will have a role in combination with other agents [besides AZT], given its efficacy in monotherapy." *Id.* at 3:13.

Also, as of March 1995, POSAs were aware of other NRTIs such as the carbocyclic guanosine analogs abacavir and carbovir. APO1006, ¶¶37-38; APO1003; APO1014, 166:3. Abacavir is a potent and selective NRTI, acts synergistically with other NRTIs, and is metabolized to (-)-carbovir triphosphate *in vivo*, which is the same metabolite to which carbovir is metabolized. APO1003; APO1016, 1004:1:1. Carbovir also is an NRTI that has potent and selective anti-HIV activity and can act synergistically with other NRTIs. APO1014, 166:3; APO1015, 2:28-31.

VIII. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review of the challenged claims of the '191 patent on the grounds for unpatentability listed in the index below. Per 37 C.F.R.

§ 42.6(d), copies of the references are filed herewith. In support of the proposed grounds for unpatentability, this Petition is accompanied by a declaration of technical expert Dr. David Katzenstein (APO1006), which explains what the art would have conveyed to a POSA.

Ground	35 U.S.C. Section (pre-3/16/2013)	Index of References	'191 Patent Claims
1	§ 103	Cameron and Daluge	1-51
2	§ 103	Cameron, Daluge, and Johnson	1-51
3	§ 103	Cameron, Daluge and Coates	20, 25-30, and 48-51

Grounds 1-3 are not redundant, though Cameron in combination with Daluge provide a reason to combine the art to arrive at the claimed invention and provide a reasonable expectation of success. For example, Johnson provides additional reasons to combine the cited art to arrive at the claimed invention, and it enhances a POSA's reasonable expectation of success, because Johnson discloses that three-drug combinations are more effective than two-drug combinations. APO1004, 908:1:2; APO1006, ¶¶39-41 and 107-111. And Coates provides additional reasons for arriving at the claims reciting a combination of two drugs, because Coates explains that AZT has a significant side effect liability and "once employed, may have to be withdrawn" from some patients. APO1005, 1:2. Thus, given the teachings of Cameron in view of Daluge, and further in view of Coates, a POSA would have had a reason to prepare a formulation or treat an animal (e.g., a

human) with a combination of AZT/3TC and abacavir and thereafter withdraw the AZT from some patients so as to mitigate AZT's side effects. Petitioner is reasonably likely to prevail in challenging the patentability of claims 1-51 on the basis of each ground herein.

1. Ground 1: Claims 1-51 Would Have Been Obvious Over Cameron in Light of Daluge

European patent application EP 0 513 917 A1 ("**Cameron**"; APO1002) was published on November 19, 1992, names Cameron *et al.* as inventors, and is entitled "Antiviral combinations containing nucleoside analogs." Cameron is prior art to the '191 patent under 35 U.S.C. § 102(b) because it published on November 19, 1992.

Prior art references must be "considered together with the knowledge of one of ordinary skill in the pertinent art." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In that regard, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). That is because an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

Cameron teaches the use of the NRTIs 3TC and AZT in combination to treat HIV patients, and it teaches that 3TC "exhibits unexpected advantages when used in combination with known inhibitors of HIV replication." APO1002, 4:20-21; APO1006, ¶¶33-36. Specifically, Cameron discloses "a synergistic antiviral effect and/or a reduction in cytotoxicity when [3TC is] used in combination with known inhibitors of HIV replication . . . , especially AZT." APO1002, Fig.1 and 4:22-36. A POSA would have understood that the 3TC/AZT drug combination taught by Cameron was one of the most effective anti-HIV treatments available. APO1006, ¶42-43 and 137. Additionally, Cameron teaches that the 3TC/AZT combination can be used with "other therapeutic and/or prophylactic ingredients." APO1002, 6:2-5.

In connection with the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy from Oct. 4-7, 1994, Daluge *et al.* published "1592U89 Succinate – A Novel Carbocyclic Nucleoside Analogue with Potent, Selective Anti-HIV activity" (**"Daluge";** APO1003). Daluge qualifies as prior art under 35 U.S.C. § 102(b) because it was published on October 5, 1994.

Daluge teaches that the NRTI known as abacavir succinate, which is also known as 1592U89 succinate, has potent and selective anti-HIV activity. APO1003. Daluge discloses that abacavir was "equivalent in potency to AZT" when tested *in vitro* in human peripheral blood lymphocytes against HIV1. *Id.* And

Daluge states that it "shows promise as a safe and efficacious treatment for HIV infection." *Id.* Daluge teaches that abacavir acts synergistically in *in vitro* assays with AZT, ddI or ddC. *Id.* And Daluge reports that abacavir shows "good oral bioavailability" in the anticipated therapeutic dose range, and that it shows 300-fold less toxicity than AZT in an *in vitro* assay. *Id.* Daluge also reports that abacavir is metabolized to (-)-carbovir triphosphate, which is the same metabolite to which carbovir is metabolized. APO1003; APO1016, 1004:1:1. Daluge notes that abacavir was comparable to AZT in its ability to penetrate into cerebral spinal fluid and brain when tested in animal models. APO1003. Thus, Daluge teaches that abacavir was a promising new treatment for HIV infection, including in combination therapy. APO1006, ¶37-38.

The petition discusses the independent claims first, before turning to the dependent claims.

Independent Claims 1 and 16: Independent claims 1 and 16 would have been obvious over the combination of Cameron and Daluge as shown below.

Claim 1	**Disclosure of Cameron and Daluge**
A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal	**Daluge:** teaches "treatment for HIV infection" (APO1003) **Daluge**: "(1592U89) [abacavir] succinate is an attractive candidate for clinical evaluation in HIV-infected patients" (APO1003) **Cameron**: "The compound of formula (I) … has been described as having antiviral activity in particular against the human immunodeficiency viruses…." (APO1002,

Claim 1	Disclosure of Cameron and Daluge
	3:28-44) **Cameron**: "the compound of formula (I) and, in particular its (-)-enantiomer [3TC] exhibits unexpected advantages when used in combination with known inhibitors of HIV replication." (APO1002, 4:20-21)
which comprises treating said animal with a therapeutically effective amount	**Cameron**: "It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms [of HIV]." (APO1002, 4:15-16) **Cameron**: "It is expected that the present combinations will be generally useful against viral infections … in humans" (APO1002, 5:24-25) **Daluge**: "Pharmacokinetic evaluation should good oral bioavailability … in the anticipated therapeutic dose range." (APO1003)
of a combination comprising [abacavir] or a physiologically functional derivative thereof,	**Cameron**: "it is preferable to present combinations as a pharmaceutical formulation." (APO1002, 5:58-6:1) **Cameron**: "The use of combinations of compounds may give rise to an equivalent antiviral effect with reduced toxicity, or an increase in drug efficacy if synergy between compounds occurs" (APO1002, 3:14-15) **Cameron**: in addition to 3TC and AZT, combinations of compounds can include "other therapeutic and/or prophylactic ingredients" (APO1002, 6:2-5) **Daluge**: "(1592U89) [abacavir] succinate is an attractive candidate for clinical evaluation in HIV-infected patients" (APO1003)
zidovudine [also known as AZT] or a physiologically functional derivative	**Cameron**: "We have now found that the compound of formula (I) and, in particular its (-)-enantiomer [3TC] exhibits unexpected advantages when used in combination with known inhibitors of HIV replication. In particular the compound of formula (I) shows a synergistic antiviral

Claim 1	Disclosure of Cameron and Daluge
thereof, and	effect and/or a reduction in cytotoxicity when used in combination with known inhibitors of HIV replication . . . especially, AZT." (APO1002, 4:20-36) **Daluge**: "[abacavir] demonstrated synergistic activity against HIV 1 when tested in combination with AZT, ddI, or ddC" (APO1003)
[3TC] or a physiologically functional derivative thereof.	**Cameron**: "We have now found that the compound of formula (I) and, in particular its (-)-enantiomer [3TC] exhibits unexpected advantages when used in combination with known inhibitors of HIV replication. In particular the compound of formula (I) shows a synergistic antiviral effect and/or a reduction in cytotoxicity when used in combination with known inhibitors of HIV replication . . . especially, AZT." (APO1002, 4:20-36)
	Cameron: "The invention thus further provides a pharmaceutical formulation comprising 3TC or a pharmaceutically acceptable derivative thereof and AZT together with one or more pharmaceutically acceptable carriers therefor" (APO1002, 6:2-4)

Claim 16	Disclosure of Cameron and Daluge
A pharmaceutical formulation comprising [abacavir] or a physiologically functional derivative thereof,	**Daluge:** teaches "treatment for HIV infection" (APO1003) **Daluge**: "(1592U89) [abacavir] succinate is an attractive candidate for clinical evaluation in HIV-infected patients" (APO1003) **Daluge**: "[abacavir] demonstrated synergistic activity against HIV 1 when tested in combination with AZT, ddI, or ddC" (APO1003) **Daluge**: "Pharmacokinetic evaluation should good oral bioavailability … in the anticipated therapeutic dose range." (APO1003) **Cameron**: "It is expected that the present combinations will be generally useful against viral infections … in

Claim 16	Disclosure of Cameron and Daluge
	humans" (APO1002, 5:24-25) **Cameron**: "it is preferable to present combinations as a pharmaceutical formulation." (APO1002, 5:58-6:1) **Cameron**: "The use of combinations of compounds may give rise to an equivalent antiviral effect with reduced toxicity, or an increase in drug efficacy if synergy between compounds occurs" (APO1002, 3:14-15) **Cameron**: in addition to 3TC and AZT, combinations of compounds can include "other therapeutic and/or prophylactic ingredients" (APO1002, 6:2-5)
Zidovudine [also known as AZT] or a physiologically functional derivative thereof,	**Cameron**: "We have now found that the compound of formula (I) and, in particular its (-)-enantiomer [3TC] exhibits unexpected advantages when used in combination with known inhibitors of HIV replication. In particular the compound of formula (I) shows a synergistic antiviral effect and/or a reduction in cytotoxicity when used in combination with known inhibitors of HIV replication . . . especially, AZT." (APO1002, 4:20-36) **Daluge**: "[abacavir] demonstrated synergistic activity against HIV 1 when tested in combination with AZT, ddI, or ddC" (APO1003)
and [3TC] or a physiologically functional derivative thereof	**Cameron**: "We have now found that the compound of formula (I) and, in particular its (-)-enantiomer [3TC] exhibits unexpected advantages when used in combination with known inhibitors of HIV replication. In particular the compound of formula (I) shows a synergistic antiviral effect and/or a reduction in cytotoxicity when used in combination with known inhibitors of HIV replication . . . especially, AZT." (APO1002, 4:20-36)
in association with one or more pharmaceutically acceptable carriers therefor.	**Cameron**: "The invention thus further provides a pharmaceutical formulation comprising 3TC or a pharmaceutically acceptable derivative thereof and AZT together with one or more pharmaceutically acceptable carriers therefor" (APO1002, 6:2-4)

As supported by the Katzenstein declaration (APO1006), a POSA would have had a reason to combine the teachings of Cameron and Daluge to arrive at the subject matter of each of independent claims 1 and 16, and a POSA would have had a reasonable expectation of success in so doing. For example, Cameron discloses that its 3TC/AZT combination was effective in treating HIV infection. APO1002, 4:20-36. Yet, a POSA would have had a reason to use Cameron's 3TC/AZT combination in conjunction with "other therapeutic and/or prophylactic ingredients," because Cameron explicitly recommends doing so. APO1002, 6:2-5; APO1006, ¶51. And a POSA would have had a reason to choose abacavir as an additional therapeutic ingredient because Daluge shows that abacavir is potent and selective for HIV; that it acts synergistically with other NRTIs, including AZT; has good pharmacokinetics and low toxicity; is a nucleoside analog of a different base than AZT or 3TC; and penetrates the central nervous system. APO1003; APO1006, ¶¶37-38, 51-55, and 73-76. Such a triple combination drug regimen would have been expected to have increased therapeutic efficacy and inhibit the development of resistance to HIV. APO1004, 908:2; APO1006, ¶¶41 and 108-112. Thus, a POSA seeking to develop an anti-HIV therapeutic would have had a reason to combine Cameron's 3TC/AZT combination with Daluge's abacavir and use it in a method for treating or preventing the symptoms of an HIV infection, as claimed.

A POSA also would have had a reasonable expectation of success in combining Cameron's AZT/3TC combination therapy with Daluge's abacavir to produce the formulation of claim 16 and for use in the method of claim 1. APO1006, ¶¶54 and 76. Each of AZT, 3TC and abacavir was known to be a useful anti-HIV agent. APO1002, 4:20-36; APO1003; APO1014, 162:1-162:2 and 166:4. And Cameron discloses that its AZT/3TC combination has synergistic activity, while Daluge shows that abacavir acts synergistically with other NRTI's, including AZT. APO1002, 4:20-26; APO1003.

Thus, the combination of these three drugs reasonably would have been expected to be useful for treating or preventing the symptoms or effects of an HIV infection in an infected animal (e.g., in a human). APO1006, ¶¶51-55, 73-76. Additionally, Daluge teaches that abacavir has good oral bioavailability and low toxicity levels (300-fold less toxic than AZT), and that its penetration into the CNS is comparable to that of AZT. APO1003. Thus, a POSA would have reasonably expected to successfully produce a formulation containing AZT, 3TC, and abacavir, along with a carrier, as claimed, and a POSA would have had a reasonable expectation to successfully use such a formulation in a method of treating or preventing symptoms or effects of an HIV infection, as claimed. APO1006, ¶51-55, 73-76.

Petitioner notes that none of the '191 patent's claims specify any particular level of anti-HIV efficacy or any particular symptoms or effects of HIV infection that must be treated or prevented. Additionally, under the broadest reasonable interpretation, the claims do not require a synergistic effect. But, even if the claims were construed narrowly so as to require a synergistic effect, a POSA also would have had a reasonable expectation of success in achieving such a synergistic effect, because the combinations of (i) AZT and 3TC and (ii) AZT and abacavir were each known to provide a synergistic effect. APO1002, 4:20-36; APO1003; APO1006, ¶¶54, 124, and Table 1. Thus, the three-drug combination also would have reasonably been expected to provide a synergistic effect. APO1006, ¶¶121-134**.**

In sum, independent claims 1 and 16 would have been obvious over Cameron in view of Daluge, even in light of any allegations of objective indicia of non-obviousness. Objective indicia of non-obviousness are addressed with respect to all claims in Section VIII.4, below.

Freebase Formulations: (Independent claims 32 and 41): Claim 32 is an independent claim that is identical to claim 1 except that it does not recite "physiologically functional derivatives" of the AZT, 3TC or abacavir. Likewise, claim 41 is an independent claim, and it is identical to claim 16 except that it also does not recite "physiologically functional derivatives" of the AZT, 3TC or

abacavir. But such claims nonetheless would have been obvious over the combination of Cameron and Daluge, which a POSA would have combined for the reasons discussed above. Cameron discloses that its combination can include AZT *or* pharmaceutically acceptable derivatives thereof, and 3TC *or* pharmaceutically acceptable derivatives thereof. APO1002, 4:23-25. Thus, a POSA would have understood that the drug could be used in its free base form, without the need for a derivative. APO1006, ¶86, 94. Similarly, a POSA would have understood from Daluge that abacavir, not just its succinate salt, would be useful as an anti-HIV drug. APO1006, ¶86. For example, Daluge concludes that "1592U89 shows promise as a safe and efficacious treatment for HIV infection," thus not limiting its disclosure to the succinate salt form of abacavir. APO1003; APO1006, ¶86. Therefore, as discussed with respect to claims 1 and 16, a POSA likewise would have found claims 32 and 41, respectively, obvious over the combination of Cameron and Daluge.

Open-ended abacavir/3TC claims (independent claims 20 and 48 and dependent claims 25-30 and 49-51): Independent claims 20 and 48 are identical to claims 32 and 16 (discussed *supra*), respectively, except that claims 20 and 48 do not expressly recite AZT (a.k.a. zidovidine). But each of claims 20 and 48 uses the open-ended transition phrase "comprising" and thus permits inclusion of a therapeutic agent(s) in addition to the abacavir and 3TC specifically recited in the

claims. Thus, for the reasons discussed above with respect to claims 32 and 16, each of claims 20 and 48 also would have been obvious to a POSA over Cameron in view of Daluge. As explained above, a POSA would have had a reason to combine Cameron's AZT/3TC combination with Daluge's abacavir for use in methods for treating HIV, and a POSA would have had a reasonable expectation of success. Such a combination and methods for using such a combination for treating or preventing the symptoms or effects of HIV are encompassed within open-ended claims 48 and 20, respectively. Thus, independent claims 20 and 48 would have been obvious even in view of any objective indicia of non-obviousness (discussed in Section VIII.4). Likewise, claims 25-30 and 49-51, which depend or indirectly from claims 10 and 48, respectively, also would have been obvious as shown below.

Ratios of Active Ingredients (dependent claims 2-4 and 13 and independent claim 45): Claims 2-4 and 13 depend directly or indirectly from claim 1 and recite particular ranges of ratios of abacavir to AZT to 3TC. Claim 2 specifies that the abacavir, AZT, and 3TC "are present in a ratio of 1 to 20:1 to 20:1 to 10 by weight." Claim 45 recites the same range as claim 2, but claim 45 omits the recitation of "physiologically functional derivatives" of the AZT, 3TC or abacavir," as discussed above for claims 32 and 41. Claims 3 and 13 limit the ratios to a range of "1 to 10:1 to 10:1 to 5 by weight." And claim 4 limits the ratios

to a range of "1 to 3:1 to 3:1 to 2 by weight." Notwithstanding the recitation of these particular ranges of ratios of the three drugs, each of claims 2-4, 13, and 45 would have been obvious over the combination of Cameron and Daluge.

For the reasons discussed above with respect to claims 1 and 16, a POSA would have had a reason to combine Cameron's AZT/3TC drug combination with Daluge's abacavir. And a POSA would have used each drug at the dose at which it was individually effective because each drug is an analog for a different nucleoside. APO1006, ¶¶31, 57-64, and 124-125. Daluge teaches administering 50 mg/kg/day of abacavir. APO1003. And Cameron teaches administering between 15 and 60 mg/kg/day of each of AZT and 3TC. APO1002, 5:41-45. Using abacavir, AZT, and 3TC at these dosages provides ratios ranging from 3.3:1:1 (for the lowest preferred AZT and 3TC dosages) to 1:1.2:1.2 (for the highest preferred AZT and 3TC dosages). APO1006, ¶57. Therefore, Cameron and Daluge teach a ratio range that is subsumed completely within the range of ratios recited in each of claims 2, 3, 13, and 45 rendering each claim obvious. And even for the narrowest recited range, which appears in claim 4, Cameron and Daluge teach a range that overlaps extensively with the claimed range. The fact that the ranges disclosed in Cameron and Daluge overlap the range of ratios recited in claim 4 establishes a *prima facie* case of obviousness. *See In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

And ViiV has not established that the range recited in claims is critical or provides any unexpected results.

Additionally, a POSA would have arrived at the claimed ranges of ratios by routinely optimizing the amounts of each drug used in the combination therapy, as doing so would require no more than routine experimentation and a POSA would have desired to optimize such a result-effective variable. APO1006, ¶57-64. Generally, differences between a claimed concentration and one disclosed in the prior art will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. *See In re Aller*, 220 F.2d 454, 456 (CCPA 1955); *see also In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.") The Patent Owner, ViiV, has not shown any criticality with respect to using the recited ratios of active ingredients. Thus, the differences between the ratios recited in claims 2-4, 13, and 45 and those in Cameron and Daluge will not support the patentability of claims 2-4, 13 and 45.

Dosages and Dosage Forms (dependent claims 5, 6, 14, 15, 17, 18, 25, 26, 33, 34, 43, 44, 46, 47, 50 and 51): Various claims of the ’191 patent contain limitations directed to the dosage of abacavir, AZT, and 3TC. Claims 5, 14, 25 and

33 depend from claims 2, 1, 20, and 32, respectively (each discussed *supra*) and limit the dosages of each of abacavir, AZT, and 3TC to 1-1500 mg. Similarly, claims 6, 15, 26, and 34 depend from claims 2, 1, 20, and 32, respectively, and limit the dosage of each drug to 5-1000 mg.

For the reasons discussed above, a POSA would have had a reason to modify Cameron's AZT/3TC combination by adding Daluge's abacavir. Cameron teaches that "the combination is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20-1000mg, most conveniently 50-700mg of each active ingredient per unit dosage form." Cameron 5:48-50. Thus, a POSA reading Cameron together with Daluge, and who is preparing a unit dosage form containing a combination of three active ingredients, would have prepared unit dosage forms in amounts that overlap the claimed ranges, *e.g.*, 50-700 mg of each of abacavir, AZT and 3TC, as claimed. APO1006, ¶¶62-643. Thus, each of claims 5, 6, 14, 15, 25, 26, and 34 would have been obvious for the reasons discussed herein. And ViiV has not established that the range recited in claims is critical or provides any unexpected results.

For similar reasons as just discussed, claims 17, 43, 46, and 50 also would have been obvious over Cameron in combination with Daluge. Claims 17, 43, 46 and 50 depend from claims 16, 41, 45, and 48 respectively (each discussed *supra*), and further specify that the formulation is "in unit dosage" or "in unit dosage

form," without limiting the unit dosages to any particular amounts. As explained immediately above, Cameron teaches providing the drug combination in unit dosage form. APO1002, 5:48-50. Thus, claims 17, 43, 46, and 50 also would have been obvious over the Cameron in view of Daluge.

Claims 18, 44, 47, and 51 depend from claims 17, 43, 46, and 50 respectively (each discussed *supra*), and specify that the formulation is "in the form of a tablet or capsule." But these claims also would have been rendered obvious by Cameron in view of Daluge, as Cameron teaches that the "Pharmaceutical formulations … may conveniently be presented as discrete units such as capsule, cachets or tablets…." APO1002, 6:14-15. And capsules and tablets are widely used dosage forms for pharmaceuticals such that a POSA would have had a reason to prepare capsules or tablets, and a POSA would have had reasonable expectation of success in preparing the claimed formulations as capsules or tablets, as recited in each of claims 18, 44, 47, and 51. APO1006, ¶78.

Formulation of Drugs (dependent claims 7, 12, 19, 35, 40, 42, and 49): Claims 7, 12, 19, 35, 40, 42, and 49 depend from claims 2, 1, 16, 32, 32, 41, and 48 respectively, (each discussed *supra*) and specify that the abacavir is the "succinate salt." Each of these claims would have been obvious over Cameron in view of Daluge. A POSA would have combined Cameron with Daluge, as discussed above. And Daluge would have provided a POSA with a reason to use abacavir succinate

because Daluge's title states that "1592U89 Succinate" has "Potent, Selective Anti-HIV Activity." APO1003; APO1006, ¶65. And the abstract states that abacavir succinate is an "attractive candidate for clinical evaluation in HIV-infected patients." APO1003. Therefore, a POSA combining Cameron and Daluge would have had a reason to use abacavir succinate and would have had a reasonable expectation of success. APO1006, ¶65. Each of claims 7, 12, 19, 35, 40, 42, and 49 would have been obvious.

Mode of Administration (claims 8-10, 21-23, 27, 28, 29, and 36-38): Claims 8, 21, 27, and 36 depend from claims 2, 1, 20 and 32, respectively, (each discussed *supra*) and require that "the combination is administered simultaneously." Similarly, claims 9, 22, 28, and 37 depend from claims 2, 1, 20, and 32, respectively, and require that "the combination is administered sequentially." Claims 10, 23, 29, and 38 also depend from claims 2, 1, 20, and 32, respectively, and require that "the combination is administered as a single combined formulation." But none of these limitations would have rendered these claims patentable over Cameron in view of Daluge. APO1006, ¶66. Cameron explicitly teaches that any of these methods of administration can be used, stating that "[i]t will be appreciated that the compound of formula I [3TC] and the second antiviral agent [AZT] may be administered either simultaneously, sequentially or in combination." APO1002, 5:32-33. Cameron also notes that combinations can

take the form of a single combined formulation, particularly "a pharmaceutical formulation comprising a compound of formula I [3TC] or a pharmaceutically acceptable derivative thereof and inhibitor of HIV replication [AZT] together with one or more pharmaceutically acceptable carriers therefor" and other therapeutic ingredients. APO1002, 6:2-4. Thus, each of claims 8-10, 21-23, 27-29, and 36-38 would have been obvious over Cameron in view of Daluge.

Treating humans (claims 11, 24, 30, and 39): Claims 11, 24, 30, and 39 depend from claims 2, 1, 20, and 32, respectively (each discussed *supra*) and further specify that the treated animal is "a human." But such methods for treating humans would have been obvious over Cameron in view of Daluge. As discussed above, a POSA would have had a reason to add Daluge's abacavir to Cameron's AZT/3TC combination. And a POSA would have had a reason to use such to use such formulations in methods for treating humans, because Cameron explicitly notes that "[i]t is expected that the present combinations will be generally useful against viral infections . . . in humans." APO1002, 5:24-25; APO1006, ¶67. Additionally, Daluge states that abacavir succinate is an "attractive candidate for clinical evaluation in HIV-infected patients." APO1003. And, Daluge reports that abacavir was "equivalent in potency to AZT when tested *in vitro* in human peripheral blood lymphocytes against fresh clinical isolates of HIV 1 from AZT-naïve patients." APO1003. A POSA reading Cameron in light of Daluge thus

would have had a reason to treat humans with a combination of AZT/3TC and abacavir as claimed. APO1006, ¶67.

A POSA also would have had a reasonable expectation of success in treating the symptoms or effects of HIV in a human in light of Cameron's disclosure that 3TC shows "a synergistic antiviral effect and/or or a reduction in cytotoxicity" when used in combination with AZT. APO1002, 4:20-36; APO1006, ¶67. And Daluge discloses that abacavir has potent and selective anti-HIV activity, starting that it's "an attractive candidate for clinical evaluation in HIV-infected patents" and that it "shows promise as a safe and efficacious treatment for HIV infection." APO1003. A POSA would have had a reasonable expectation of success in using the combination of AZT/3TC and abacavir in treating humans. APO1006, ¶67. Notably, none of the '191 patent claims requires any particular level of efficacy.

Patient Pack (Claim 31): Claim 31 is an independent claim directed to a patient pack comprising "at least one" active ingredient selected from abacavir, AZT, and 3TC, and the patient pack further comprises "an information insert containing directions on the use of all three active ingredients together in combination." Such a patient pack would have been obvious over Cameron in view of Daluge. Under the broadest reasonable interpretation, only a single active ingredient needs to be provided in the patient pack in conjunction with the information insert.

Under the printed matter doctrine, written instructions on how to use a drug or drug combination will not distinguish a composition from the prior art unless it is "functionally related" to the composition itself. *See AstraZeneca LP v. Apotex Corp.*, 633 F.3d 1042, 1063 (Fed. Cir. 2010). For instance, the Federal Circuit has held that a package label instructing on a method of using a drug composition was "not entitled to patentable weight [because] [t]he instructions in no way function with the drug." *Id.* at 1065. *See* also, *In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004) (holding that instructions on use of a kit were not a meaningful limitation because "[a]ll that the printed matter does is teach a new use of an existing product"). This precedent clearly indicates that instructions on using the three drugs in combination cannot distinguish an otherwise obvious product from the prior art. Therefore, claim 31 would have been obvious over Cameron in view of Daluge.

And, even if the contents of the information insert were considered in assessing obviousness, the claims nonetheless would have been obvious over Cameron in view of Daluge. These prior art references would have provided a reason for a POSA to prepare a patient pack as claimed because the art rendered obvious the combination of AZT/3TC and abacavir, and patient packs provide convenience and minimize confusion for patients. APO1006, ¶82. And a POSA would have included in the patient pack instructions for using the three active

ingredients together in combination so as to minimize confusion for patients. *Id.* And a POSA would have had a reasonable expectation of success because producing such a patient pack is well within the level ordinary skill in the field. *Id.*

2. Ground 2: Claims 1-51 Would Have Been Obvious Over Cameron in View of Daluge and Johnson

Cameron and Daluge are discussed above in Ground 1. On August 26, 1994, Johnson published a review article entitled "Combination Therapy: More Effective Control of HIV Type I?" in the journal *AIDS Research and Human Retroviruses* (**"Johnson"**; APO1004). Like Cameron and Daluge, Johnson qualifies as prior art to the '191 patent under 35 U.S.C. § 102(b). Johnson discloses that "the rationale for combining anti-HIV-1 agents is to provide more complete viral suppression, to limit the emergence of drug resistance … and to provide more effective antiretroviral treatment…." APO1004, Abstract. Johnson also discloses that "*In vitro* studies demonstrate that three-drug regimens delay breakthrough of HIV-1 replication more effectively than two-drug regimens or single-drug regiments." APO1004, 908:1:2. And Johnson states that "three reverse transcriptase inhibitors . . . could be used in combination regimens." APO1004, 908:1:4.

A POSA looking to develop an anti-HIV therapeutic would have had a reason to combine the teachings of Cameron, Daluge, and Johnson, as all three references are directed to anti-HIV therapeutics involving a combination of reverse transcriptase inhibitors. As discussed above, a POSA would have had a reason to

combine Cameron's AZT/3TC combination with a further anti-HIV therapeutic, such as Daluge's abacavir, to arrive at the subject matter of claims 1-51. Indeed, Cameron explicitly suggests combining its AZT/3TC with a further anti-HIV therapeutic. APO1002, 6:2-5. And the petition explains in detail under Ground 1 that a POSA would have had sufficient reason to combine Cameron's AZT/3TC combination with Daluge's abacavir, and why such a POSA would have had a reasonable expectation of success for each of claims 1-51.

The rationales provided under Ground 1 are fully applicable to Ground 2 as well. And under Ground 2, Johnson provides even more reason to combine Cameron's AZT/3TC combination with Daluge's abacavir to arrive at the claimed invention, because Johnson discloses that three-drug combinations are more effective than two-drug combinations. APO1004, 908:1:2; APO1006, ¶¶39-41 and 107-111. For the same reason, Johnson also provides a further basis for having a reasonable expectation of success in combining Cameron's AZT/3TC combination with Daluge's abacavir. APO1006, ¶¶108-112. Additionally, abacavir, which is an analog of guanosine, acts independently of AZT and 3TC, which are analogs of thymine and cytosine, respectively. APO1003; APO1017; APO1014, 162:2 and 166:3-4; APO1006, ¶¶31, 110, and 124-125. Thus, abacavir in combination with AZT and 3TC meets Johnson's suggestion that the antiviral agents act independently. APO1004, 908:4; APO1006, ¶110.

Thus, a POSA reading Cameron in view of Daluge and further in view of Johnson would have had a reason to combine the teachings of the references to arrive at the subject matter of claims 1-51, and such a POSA would have had a reasonable expectation of success. APO1006, ¶¶108-112. Each of claims 1-51 would have been obvious over the combination of Cameron, Daluge and Johnson even in light of any allegations of objective indicia of nonobviousness (discussed further in Section VIII.4).

3. Ground 3: Claims 20, 25-30, and 48-51 Would Have Been Obvious Over Cameron in view of Daluge and further in view of Coates

Claims 20, 25-30, and 48-51 recite formulations comprising abacavir and 3TC, and methods comprising treating an HIV-infected animal with a therapeutically effective amount of a combination comprising abacavir and 3TC. As discussed above, each of claims 20, 25-30, and 48-51 uses the open-ended transition phrase "comprising" and thus permits inclusion of a therapeutic agent(s) in addition to the agents specifically recited in the claims. Accordingly, for the reasons explained above under Ground 1, it would have been obvious to combine Cameron's AZT/3TC combination with Daluge's abacavir to arrive at the subject matter of claims 20, 25-30, and 48-51, since Cameron states that its AZT/3TC combination could be used with other therapeutic and/or prophylactic ingredients, and Daluge shows that abacavir is a potent and attractive anti-HIV drug. As shown

below, each of claims 20, 25-30, and 48-51 also would have been obvious to a POSA over Cameron in view of Daluge and further in view of **"Coates"** (APO1005).

Coates was published as WO 91/17159 on November 14, 1995 and thus qualifies as prior art under 35 U.S.C. § 102(b). Coates discusses 3TC, which is also known as (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one). APO1001, 1:12-14; APO1005, 2:2-3. Coates discloses that 3TC has antiviral activity against HIV and lower toxicity than the other enantiomer of the same chemical formula. APO1005, 1:1 and 2:2-3. Coates also notes that while AZT has been approved for treatment in HIV patients, it has "a significant side-effect liability and thus either cannot be employed or, once employed, *may have to be withdrawn* in a significant number of patients." APO1005, 1:2 (emphasis added). Coates also teaches that pharmaceutically acceptable derivatives of 3TC may be used. APO1005, 2:2. Additionally, Coates teaches that 3TC may be used together with another antiviral agent(s), including a nucleoside analog such as AZT. APO1005, 8:4-5 and 7. Coates also discloses that the 3TC can be formulated together with a carrier. APO1005, 6:1.

For the reasons discussed above under Ground 1, a POSA would have had a reason to combine Cameron's AZT/3TC combination with Daluge's abacavir, because Cameron suggests including an additional therapeutic agent, and abacavir

was recognized as a potent and attractive anti-HIV drug. A POSA reading Cameron and Daluge also would have had a reason to consider the teachings of Coates, because Coates provides an extensive discussion of the use of 3TC for treating HIV infections, both alone and in combination with other therapeutics, including AZT. APO1006, ¶¶113-118. A POSA reading Cameron in view of Daluge and further in view of Coates would have understood that AZT, "once employed, may have to be withdrawn" due to side effects of AZT. APO1005, 1:2; APO1006, ¶116. Thus, given the teachings of Cameron in view of Daluge and Coates, a POSA would have had a reason to prepare a formulation and treat a patient with a formulation comprising AZT/3TC and abacavir. APO1006, ¶116. And in view of Coates's disclosure of the side effects of AZT, a POSA would have had a further reason, after employing the AZT/3TC/abacavir combination, to withdraw the AZT from some patients so as to mitigate AZT's side effects. *Id.* Thus, a POSA would have had a reason in view of Cameron, Daluge and Coates to arrive at the subject matter of claims 20 and 48, which recite combinations of 3TC and abacavir, but are open to inclusion of additional therapeutics. *Id.*

And a POSA would have had a reasonable expectation of success because Cameron, Daluge and Coates teach that each of 3TC and abacavir (as well as AZT) has potent anti-HIV activity. APO1002, 4:20-21, APO1003, APO1005, 2:2; APO1006, ¶117. And Cameron and Coates each suggest that 3TC be used in

combination with a an additional anti-HIV agent, whereas Daluge recognizes that abacavir has potent, selective anti-HIV activity, with less toxicity than AZT and good oral bioavailability while also penetrating the CNS. APO1002, 6:2-5, APO1003, APO1005, 8:4-5, 7; APO1006, ¶117. Moreover, the claims do not require any particular level of efficacy, nor do they require a synergistic effect. Each of independent claims 20 and 48 would thus have been obvious over Cameron in view of Daluge and further in view of Coates.

Claims 25-30 and 49-51 depend or indirectly from claims 20 and 48, respectively. The limitations added by these dependent claims are discussed in detail under Ground 1. And, as explained under Ground 1, none of these added limitations distinguishes claims 25-30 and 49-51 over Cameron in view of Daluge. Likewise, none the limitations added to claims 25-30 or 49-51 distinguish those claims from the teachings of Cameron in view of Daluge and further in view of Coates. Accordingly, each of claims 20, 25-30, and 48-51 would have been obvious over Cameron in view of Daluge and further in view of Coates, even in view of any objective indicia of nonobviousness (discussed below).

4. Objective indicia of nonobviousness

ViiV may attempt to avoid a finding of obviousness by asserting the secondary considerations it alleged during *ex parte* prosecution and during district

court litigation ("the Teva/Lupin litigation").[1] Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). And in cases where a strong obviousness showing exists, the CAFC has repeatedly held that even relevant secondary considerations supported by substantial evidence may not dislodge the primary conclusion of obviousness. *See, e.g., Leapfrog Enterprises Inc. v. Fisher-Price Inc*., 485 F.3d 1157, 1162 (Fed. Cir. 2007).

As discussed below, ViiV's arguments regarding secondary considerations do not support patentability. First, ViiV's arguments of secondary considerations were provided largely through factually-unsupported opinion testimony, and therefore have little evidentiary value. *In re Beattie*, 974 F.2d 1309 (Fed. Cir. 1992); *Ex parte George*, 21 USPQ2d 1058 (B.P.A.I. 1991) (conclusory statements unsupported by objective factual evidence are not given substantial evidentiary value). Second, ViiV's secondary-considerations arguments fail for both factual and legal reasons, discussed below. So the Board should accord ViiV's arguments little weight, if any.

Third, the Board is not bound by any determination made by the district

[1] *ViiV Healthcare UK Ltd., et al. v. Lupin Ltd., et al.*, C.A. No. 11-576-RGA (D.Del.), not involving Petitioner.

court in a prior litigation involving the ‘191 patent, particularly since the Petitioner was not involved in that litigation. And, of course, the Board is not bound by the determinations of the Examiner made during the prosecution of the '191 patent. For the reasons articulated herein, even in view of ViiV's arguments of regarding objective indicia, the claims of the ’191 patent would have been obvious.

a) No Unexpectedly Superior Results

(1) ViiV’s in vitro synergy evidence does not support patentability

"[W]hen unexpected results are used as evidence of non-obviousness, the results must be shown to be *unexpected* compared with the closest prior art." *In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991), *citing In re De Blauwe*, 736 F.2d 699, 705 (Fed.Cir. 1984). Thus, any factual evidence of unexpectedly superior results presented by ViiV must establish that the alleged invention in the challenged claims achieved unexpectedly superior results with respect to the results of the closest prior art. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Objective evidence must be attributable to the claimed invention, and aside from what is unclaimed or in the prior art. *In re Kao*, 639 F.3d at 1068 ("Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.")

ViiV's *in vitro* synergy evidence fails on both grounds. First, ViiV failed to make a comparison of its results to the closest prior art. And, when such comparison is properly made, it is evident that ViiV's alleged unexpectedly superior results are illusory. And, second, ViiV's allegations of *in vitro* synergy fail to satisfy the nexus requirement. Both of these failures are addressed below:

(2) ViiV's in vitro synergy evidence would not have been unexpected

During prosecution of the '191 patent, Ms. St. Clair, an inventor, presented a declaration containing data from *in vitro* testing of the claimed triple combination of AZT/3TC/abacavir. APO1033, 220-243. Ms. St. Clair alleged that "the triple combination of zidovudine [AZT], 3TC and [abacavir] was synergistic in suppression of viral replication in lymphocytes *in vitro*." APO1033, 221:¶8. And Ms. St. Clair alleged that the synergistic effect was "unexpected" because each of the three claimed drugs shared the same viral target. APO1033, 221-222:¶9. The first flaw in Ms. St. Clair's argument is that the three drug's don't have the same target, as they each compete with different nucleosides for binding to different reverse transcriptase-RNA template complexes. APO1006, ¶¶31, 124-125.

Second, Ms. St. Clair never established that the results were unexpected over the closest prior art drug combinations, *which also show synergy.* APO1002, 4:20-36; APO1003, APO1019, 223:1:2-224:1:2 (noting that synergy was "generally expected" between anti-HIV agents so long as the drugs operate by different

mechanisms). As summarized in Table 1 below, combinations of the drugs recited in the claims were known to show synergy.

Table 1. Prior art taught *in vitro* synergy of pairs of the claimed drugs.

HIV Drug	**Synergy With:**		
	AZT	**3TC**	**Abacavir**
AZT	N/A	YES[2]	YES[3]
3TC	YES[2]	N/A	Not reported
Abacavir	YES[3]	Not reported	N/A

Third, the *in vitro* synergy data presented by ViiV would not have been unexpectedly *superior* compared with the closest prior art.

For claims 1-19, 21-24 and 31-47 (the three-drug claims), the closest prior art is Cameron. Cameron teaches that combinations of 3TC and AZT have a synergistic antiviral effect. APO1002, 3:22. In Example 2, Cameron provides data demonstrating that 3TC and AZT have synergistic activity *in vitro*. APO1002, 10:11-20 and Figure 1. And Cameron also shows that combinations of AZT and ddI (another NRTI acting at the same viral target) have synergistic activity *in vitro*.

[2] APO1002, 4:20-26; APO1011, 2:1; APO1012, 11:2:6; APO1013, 2:6-3:2.

[3] APO1003.

See e.g. APO1002, 10:14-17 and Figure 3. It would not have been surprising to a POSA that a three-drug combination—including two drugs known to act synergistically—would also display synergy. APO1006, ¶¶121-134. For example, Mazzulli *et al*. (APO1032), published in 1993, describes a study of combinations of NRTIs, including three NRTIs. APO1006, ¶126.

Even if the Board considers Daluge to be the closest prior art for the three-drug claims, ViiV's results are not unexpectedly superior over that art either. Daluge explicitly taught that abacavir "demonstrated synergistic activity against HIV when tested in combination with AZT." APO1003. Given such data, it would *not* have been unexpected to a POSA that a three-drug combination including 3TC, AZT, and abacavir would have synergistic activity *in vitro*. APO1006, ¶¶31, 124-125.

Furthermore, regardless of which art is chosen as closest, a POSA would have been aware that each drug was known to have synergistic activity *in vitro* when combined with another drug of the three-drug combination. *See* Table 1, summarizing the known *in vitro* synergy of AZT, 3TC, and abacavir.

A POSA would have been aware of the art summarized in Table 1 and therefore would not have found *in vitro* synergy in a three-drug combination of 3TC, AZT, and abacavir unexpected. APO1006, ¶¶121-130. In view of this prior

art, ViiV has not established — and cannot establish— that the claimed invention exhibits unexpected synergy when compared to closest prior art.

Similarly, for claims 20, 25-30 and 48-51 (the two-drug claims), it would not have been surprising to a POSA that the combination of abacavir and 3TC would have been synergistic *in vitro,* because it was established that abacavir and 3TC acted synergistically *in vitro* when combined with another antiviral (AZT) acting on the same viral target. *See* APO1002, Example 2; APO1006 ¶129-130. So even if ViiV provided data showing *in vitro* synergy of 3TC and abacavir compared to the closest prior art, such synergy would not have been unexpected to a POSA. APO1006, ¶¶129-130.

In view of the *in vitro* synergy evidence in the prior art, claims 1-51 would have been obvious notwithstanding any alleged unexpected results.

b) ViiV's Alleged Evidence of Unexpected Clinical Efficacy Should Be Given Little Weight, if Any

During prosecution and also in district court, ViiV asserted that the triple combination of 3TC, AZT, and abacavir and the double combination of 3TC and abacavir were unexpectedly clinically superior to AZT/3TC. APO1033, Response to Office Action dated Sept. 14, 1999; APO1029, 37. ViiV argued that the clinical efficacy of the two-drug and three-drug combinations would have been surprising to a POSA. APO1033, Response to Office Action, mailed September 14, 1999 at 3; APO1029, 37. But ViiV has not shown any unexpected clinical superiority of the

two or three-drug combination compared to the closest prior art. ViiV's evidence does not comport with the requirements for showing *unexpectedly superior* results over the prior art. *In re Eli Lilly & Co.*, 902 F.2d 943, 948 (Fed. Cir. 1990).

For the 3TC/abacavir combination, ViiV relied principally on one clinical study protocol to allege unexpected clinical efficacy. But this study at best showed only that this drug combination was *not inferior* to the prior art; it did not show unexpectedly *superior* results. Specifically, CNA30024 (APO1020) was a clinical study in adults treated with abacavir/3TC and Efavirenz (an NNRTI) or the prior art combination of AZT/3TC and Efavirenz. The authors of the study concluded that both treatment arms were statistically *equivalently* effective. APO1020; APO1006, ¶132. "In conclusion, data from this study demonstrate that this abacavir-based regimen confers durable antiviral response over a 48-week period of therapy, *which is comparable to the current standard of care*." APO1020, 1045:1:5 (emphasis added).

ViiV's own expert at trial admitted that the comparison showed only that the two-drug composition of abacavir/3TC was "non-inferior" to the prior art AZT/3TC treatment when combined with Efavirenz. APO1023, 154:1-5. Thus, there was no showing of *unexpectedly superior* results for the claimed two-drug combination.

At trial, for the three-drug combination, ViiV relied on a pediatric study comparing various clinical parameters in children taking either the double combination of AZT/3TC or the triple combination of AZT, 3TC, and abacavir. APO1021. The authors of the pediatric study wrote, "*[a]s expected* . . . the degree of viral suppression provided by the [abacavir]/3TC/[AZT] regimen was *modest*, while the improvement in immune response was moderate." APO1021, 8:1:3-8:2:1 (emphasis added). Such modest differences between the claimed invention and what was expected in view of the art are not *unexpectedly superior* and cannot show non-obviousness of the claims in view of the prior art. Thus, the claims would have been obvious even in light of the clinical evidence available.

Similarly, during prosecution, ViiV provided abstracts of clinical studies to support its alleged unexpectedly superior results. But one abstract states "There was no significant difference between the two treatment groups over time." APO1033, Response to Office Action, mailed September 14, 1999 at 5. And another abstract concludes, "Antiviral efficacy & CD4 response with [abacavir]/3TC/[AZT] is *equivalent* to IDV/3TC/[AZT] after 24 weeks of therapy in the 48-week study in ART naïve adults." APO1033, Response to Office Action, mailed September 14, 1999 at 7 (emphasis added). Thus, ViiV's data do not establish unexpected clinical efficacy and must therefore fail.

c) No Long-Felt and Unmet Need or Failure of Others

A showing of a long felt and unmet need requires three factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539 (CCPA 1967). Second, the long-felt need must not have been satisfied by another before the invention by applicant. *Newell Companies v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Third, the invention must in fact satisfy the long-felt need. *In re Cavanagh*, 436 F.2d 491, (CCPA 1971). ViiV's evidence fails on all three counts.

There was no persistent, unmet need in the art for the claimed invention. In its post-trial brief, ViiV, attempting to define the need, stated that in 1995, "the AIDS epidemic was a dire health crisis [and] *few effective drugs existed* in March 1995." APO1029, 37:1 (emphasis added). But ViiV's statement itself indicates that effective drugs to treat HIV were on the market. Indeed, there were many HIV drugs available as of March 1995 including ddI, ddA, ddC, AZT, 3TC, and others, as well as combinations of these drugs. *See generally*, APO1004, APO1010; APO1019. Both monotherapies and combination therapies were used to treat HIV infections. APO1004, 910:1:3-910:2:2; APO1006, ¶¶29-31, 136. Furthermore, the claims of the '191 patent do not require any particular level of treatment efficacy. APO1001, claims. Rather, the claims only require "a method for the treatment or

prevention of the symptoms or effects of an HIV infection" and such treatment methods were available before March 1995.

ViiV's blanket allegation—that there "were few effective drugs" —does not rise to the level of long-felt need. *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009); *see also, In re Kahn*, 441 F.3d 977, 990-91 (Fed. Cir. 2006) ("our precedent requires that the applicant submit actual evidence of long-felt need, as opposed to argument"). And ViiV has not identified any art that articulates a need for the claimed invention. Thus, the evidence of record does not establish that there was a persistent need recognized in the art.

Second, the advent of the AZT/3TC combination satisfied any long-felt need alleged by ViiV. ViiV admitted that the prior art combination AZT/3TC therapy was "the gold standard" and that it was hailed as a "breath of fresh air" when successful clinical trial data showed that the prior art combination AZT/3TC dramatically enhanced clinical benefit over monotherapies. APO1029, 10:2 and 37:1; APO1012, 11:2:1; APO1013, 2:6. Therefore, any alleged need for HIV treatment was met before March 1995. (*See e.g. P & G v. Teva Pharms, USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009)(finding evidence that a prior alternative drug useful for treating osteoporosis obviated a long-felt unmet need).

Third, even if there had been a need in the art for improved therapies after the introduction of AZT/3TC combination therapy, that need was not solved by the

subject matter of the claims of the ’191 patent. The CAFC has articulated that there must be actual evidence “presented that the claimed invention actually satisfied the purported long-felt need.” *In re Gardner*¸ 449 Fed.Appx. 914, 918 (Fed. Cir. 2011). ViiV alleged that “[t]he inventions of the ’191 patent provided great clinical efficacy and prolonged lives.” APO1029, 34:1. But as discussed above, the clinical efficacy of the two-drug combination and three-drug combination was, “comparable to the current standard of care,” “non-inferior” and “modest.” *See e.g.* APO1020, 1045:1:5; APO1023, 154:1-5; APO1021, 8:1:3-8:2:1, discussed above. Therefore, ViiV cannot show that the claimed inventions satisfied any need for an improved anti-HIV therapy. For at least these reasons, the claimed embodiments of the ’191 patent did not meet a long felt and unmet need sufficient to support non-obviousness of the claims.

Similarly, ViiV cannot rely on failure of others to develop formulations or methods for the treatment or prevention of the symptoms or effects of an HIV infection. As noted above, efficacious HIV drugs were available as of March 1995 including ddI, ddA, ddC, AZT, 3TC, as well as combinations of these drugs. APO1004, 909-910; APO1005, 1:2; APO1010; APO1019. And each of these drugs was capable of treating or preventing the symptoms or effects of an HIV infection. APO1004, 909-910; APO1005, 1:2; APO1006, ¶139; APO1025, 1929-1935. And the prior art combination AZT/3TC therapy was particularly successful as it

provided long lasting clinical benefit. APO1012, 11:2:1. Such successes in the prior art negate any of Viiv's efforts to rely upon allegations of failures of others.

d) No Skepticism by Experts

Evidence of skepticism must directly address whether there was actual skepticism concerning the claimed invention. *Dow Jones & Co. v. Ablaise Ltd*., 606 F.3d 1338, 1352 (Fed. Cir. 2010). And the patentee must establish that a nexus exists between the alleged skepticism and the claimed invention. *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327-28 (Fed. Cir. 2008). But in asserting skepticism, ViiV cannot show that there was any skepticism that the claimed combinations would treat or prevent the symptoms or effects of HIV as recited in the claims. APO1006, ¶140. At trial, ViiV relied on a statement from a coworker of the inventors who wrote in an *internal* communication that 3TC and abacavir "clearly show some cross resistance." APO1024, 144:5-145:23. ViiV's proffered evidence of a single comment by a single coworker is far from the required actual and direct skepticism by experts concerning the claimed invention's *feasibility*. *See Dow Jones & Co., Inc. v. Abalaise Ltd.*, 606 F.3d 1338, 1352 (Fed. Cir. 2010).

ViiV also relied on was a statement of a clinical trial review board noting "that the combination [of 3TC and abacavir]. . . *might* not provide a potent or sustainable reduction of HIV-1 RNA in plasma. . . ." APO1029, 38:2 (emphasis added). However, ViiV failed to establish that a nexus exists between the alleged

skepticism and the claimed invention. *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327-28 (Fed. Cir. 2008). As discussed above, the claims do not recite any particular level of efficacy. And ViiV never provided evidence that experts thought the claimed combinations would be insufficient to treat or prevent symptoms or effects of HIV. APO1006, ¶140. Thus, even in view of ViiV's allegations of skepticism of experts, the claims of the '191 patent would have been obvious.

e) No Commercial Success

Commercial success requires that the success of the claimed product must have "resulted from the merits of the claimed invention as *opposed to the prior art or other extrinsic factors*." *In re Kao*, 639 F.3d at 1070 (emphasis added). In other words, the patent owner must "link" the commercial success with features of the invention not shown in the prior art. *Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008). In district court, in an effort to make its market share appear to be significant, ViiV narrowly construed the market to be limited to NRTIs. But there are a variety of drugs that treat or prevent the symptoms or effects of HIV invention, as recited in the claims, and thus a POSA would not limit the relevant market to NRTIs. APO1006, ¶141. In district court, ViiV did not dispute evidence that, based on prescriptions written, Epzicom (a two-drug combination) reached a peak market share of 4.9% and that Trizavir (a three-drug

combination) reached a peak market share of 5% of the market for anti-HIV therapies. APO1025, 267:22-268:4. Such a modest market share does not rise to the level of establishing commercial success of the claimed invention.

ViiV cannot show that its alleged commercial success was due to a novel feature of the claimed invention. *See Tokai Corp. v. Eason Enters., Inc.*, 632 F.3d 1358, 1369-70 (Fed. Cir. 2011). Nor can ViiV show that some unique property of the claimed combinations drove sales. In fact, given the prior art formulations including combinations of 3TC/AZT or AZT/abacavir, any commercial success was due to an element in the prior art, rather than a novel feature of the claims. Indeed, evidence presented at trial established that, following the launch of Epzicom and Trizivir, the total sales of each of the drugs' active ingredients remained *flat*, indicating that neither combination drug sparked demand for more product. APO1025, 272:6-273:18; APO1006, ¶142. Rather, the individual drugs, which were known in the prior art, accounted for the sales of the combination products ViiV markets. APO1025, 272:6-273:18; APO1006, ¶142.

f) No Evidence of Industry Praise

In alleging industry praise at trial, ViiV asserted that the commercial embodiments have been prescribed often and have been identified by various HIV treatment guidelines. APO1034, 51:3-52:2. But ViiV's evidence falls well short of

showing industry *praise*. For example, ViiV provided no evidence that drug researchers or competitors found Epzicom or Trizavir to be superior to other known anti-HIV therapies. APO1006, ¶144. And the mere fact that an approved drug is noted as efficacious has little bearing on industry praise. *See Bayer Healthcare Pharm., Inc. v. Watson Pharm, Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013)(holding that journal articles referencing efficacy were not sufficient to show industry praise). As such, ViiV's attempts to show industry praise should be given little weight.

IX. CONCLUSION

Each of claims 1-51 would have been obvious over the art discussed above, notwithstanding any assertions of objective indicia of nonobviousness. IPR should be instituted for each challenged claim.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Eldora L. Ellison/

Date: June 2, 2014
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
202-371-2600
1830959

Eldora L. Ellison
Registration No. 39,967
Attorney for Petitioner

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 6,417,191 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123" was served in its entirety on June 2, 2014, upon the following party via EXPRESS MAIL:

GlaxoSmithKline
Global Patents
Five Moore Dr., P.O. Box 13398
Mailstop: 62111.2F
Research Triangle Park, NC 27709-3398
Patent owner's correspondence address of record for U.S. Patent No. 6,417,191

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Eldora L. Ellison/
Eldora L. Ellison (Reg. No. 39,967)
Lead Attorney for Petitioner Apotex Corp.

Date: June 2, 2014

1100 New York Avenue, N.W.
Washington, D.C. 20005 - 3934
(202) 371-2600