UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX CORP.

Petitioner

v.

ViiV HEALTHCARE CO. and ViiV HEALTHCARE UK LTD.

Patent Owners

Case IPR2014-00876

Patent 6,417,191

PATENT OWNERS' RESPONSE

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I. INTRODUCTION

Apotex has not shown by a preponderance of the evidence that any of claims 1-51 of the '191 patent are obvious. Apotex's challenge is based on impermissible hindsight and revisionist history. Apotex's Petition argues that the claimed combinations of abacavir/3TC and abacavir/3TC/AZT are obvious. Apotex impermissibly enlists the '191 patent as a roadmap to paint a picture of HIV research as limited to a handful of nucleoside reverse transcriptase inhibitors ("NRTIs"), conveniently including abacavir, 3TC, and AZT. Apotex then argues that because the three were known anti-HIV compounds, a person of ordinary skill ("POSA") would have been motivated to combine them in a triple NRTI combination with an expectation of success. A district court and the Federal Circuit have rejected these same misguided arguments based on the same references and upheld the validity of the '191 patent claims. As the district court concluded, far from being obvious, "[c]oncerns of toxicity, potency, cross-resistance profiles, HIV's ability to mutate swiftly, a large universe of potential compounds and drug classes, and rapidly dying patients…made assembling an effective drug combination extremely challenging." Ex.1034 at 64.

In 1995, HIV was a public health crisis. Researchers faced enormously complex and daunting challenges. Resistance was the primary cause of treatment failure, resulting in eventual death. Researchers began to experiment with

combination therapy to combat resistance. However, at that time there were hundreds of available anti-HIV agents, making the number of potential combinations "astronomical." Ex.2149 (Dr. Katzenstein Cross Exam. Tr.) at 57:17-21. Moreover, experience had shown an unpredictable field, and combinations more so. By March 1995, all but one combination had failed to show any benefit over monotherapy. Again, resistance was the primary culprit. Further, because many of these compounds alone caused serious, often debilitating toxicities, their combination proved to be even more toxic. Conventional wisdom strongly discouraged combinations such as the claimed combinations, that would likely increase toxic side effects or were likely cross resistant.

Apotex's expert admitted that he—like the Petition—had an opportunity to, but did not discuss many of the critical facts supporting patentability, including unpredictability, toxicity, the resistance profiles for abacavir and 3TC, and cross-resistance. He also admitted other critical facts buttressing the patentability of the '191 patent claims, including that a POSA designing a combination would have considered all classes of anti-HIV agents, in particular protease inhibitors ("PIs") and ("NNRTIs") because of their significant advantages, would have sought to avoid combinations that had a greater likelihood of toxic side effects, would have sought to avoid potential cross-resistance as it would lead to treatment failure, and would have known abacavir and 3TC have overlapping resistance profiles

including both selecting for the ***same primary mutation***. He further admitted that he worked with anti-HIV agents outside the NRTI class by 1995, and that, even years after the priority date, as a member of an international panel, he never recommended any triple combinations of NRTIs.

In short, Apotex's hindsight-based obviousness allegations, which simply rehash arguments made in the district court, are flawed. A POSA had ample reasons to ***avoid*** the claimed combinations and would have had no reasonable expectation of success. Further, secondary considerations, including commercial success, unexpected results, long-felt and unresolved need, industry recognition, and skepticism, support the nonobviousness of the claimed combinations. Accordingly, ViiV respectfully requests that the Board uphold the patentability of claims 1-51 of the '191 patent.

II. OVERVIEW OF THE '191 PATENT

The '191 patent, titled "Synergistic Combinations of Zidovudine, 1592U89, and 3TC" claims priority to two Great Britain patent applications filed on March 30, 1995. Ex.1001 ('191 patent) at (54), (30). The '191 patent lists David Barry and Martha ("Marty") H. St. Clair as inventors and issued on July 9, 2002. *Id*. at (75), (45).

The claims of the '191 patent are directed to (1) a combination of abacavir/3TC (independent claims 20 & 48), and (2) a combination of

abacavir/3TC/AZT (independent claims 1, 16, 31, 32, 41, 45). Various dependent claims cover, for instance, specific ratios of the active ingredients, particular dosage amounts and forms, and methods for administration.

During prosecution, the Examiner initially rejected the claims of the '191 patent as "prima facia obvious" because the recited compounds were individually known as useful for treating HIV. Ex.1033 at 118-19. Among other references, the Examiner considered both Cameron and Daluge. Ex.1001 at (56) Cited References. Applicants overcame the rejection, explaining the prior art did not disclose or suggest the claimed combinations, did not suggest their desirability, and did not provide a reasonable expectation of success. Applicants supported the validity of the claims by submitting evidence of unexpected *in vitro* synergy and clinical efficacy. The Examiner then allowed the claims. Ex.1033 at 265-66.

III. THE FEDERAL CIRCUIT HAS AFFIRMED THE VALIDITY OF THE '191 PATENT

Other generic drug manufacturers have challenged the validity of the '191 patent but have appropriately failed. *ViiV Healthcare UK Ltd. et al. v. Lupin Ltd. et al.*, Case No. 1:11-cv-00576-RGA (D. Del. filed June 29, 2011), (consolidated with *ViiV Healthcare UK Ltd. et al. v. Teva Pharmaceuticals USA, Inc. et al.*, Case No. 1:11-cv-00688-RMB (D. Del. filed August 5, 2011) on October 31, 2011). Those challenges included the same arguments Apotex makes here and relied on

the same references asserted in Ground 1. Ex.1022, 356:17-359:15 (discussing Daluge); Ex.1023, 294:15-295:19 (discussing Cameron). After a five-day trial in which the district court heard testimony from ***eleven experts***, including ViiV's declarant Dr. David Ho, the Court issued findings of fact and conclusions of law. Ex.1034. The Court's 50-page discussion of obviousness reviewed the evidence and concluded, contrary to Apotex's arguments in these proceedings, that "[t]here was very little about anti-HIV therapy that could be described as predictable as of March 1995, and the history of failure in the field offered … little reason to expect that any particular combination would work." Ex.1034 at 64. "Concerns of toxicity, potency, cross-resistance profiles, HIV's ability to mutate swiftly, a large universe of potential compounds and drug classes, and rapidly dying patients in the midst of a public health crisis," the Court found, "made assembling an effective drug combination extremely challenging." *Id*.

The Court noted that a POSA would have considered the universe of available anti-HIV agents, including PIs and NNRTIs. *Id*. at 23, 25. The Court found that "[t]he weight of the prior art most strongly suggests that concerns of cross-resistance would be a discouraging factor, even for combinations displaying significant potency and limited toxicity." *Id*. at 39. Further, the Court found that suspected cross resistance between abacavir and 3TC "provided a reason for researchers to look in another direction than a combination of those drugs." *Id*. at

43. Based on these findings, among others, the Court upheld the validity of the '191 patent. Ex.1034 at 67. On February 12, 2015, the Federal Circuit affirmed the opinion of the district court upholding the validity of the '191 patent. *ViiV Healthcare Co. v. Lupin Ltd.*, --- Fed. App'x ---, 2015 WL 573947, at *1 (Fed. Cir. 2015).

IV. IPR PROCEDURAL HISTORY

Apotex filed the Petition seeking institution of an IPR based on three different grounds. Paper 2. The Board instituted this IPR only on Apotex's Ground 1—that claims 1-51 would allegedly have been obvious over the Cameron and Daluge references. Paper 10. Importantly, Ground 1 takes the position that a POSA would take the combination of AZT/3TC (Cameron) and add abacavir (Daluge) to create a triple-NRTI combination. Ground 1 does not allege that it was obvious to combine abacavir and 3TC without AZT.

V. CLAIM CONSTRUCTION

As shown below, some of Apotex's proposed constructions are narrower than the broadest reasonable interpretation (*see* 37 C.F.R. § 42.100(b)), or contrary to the plain and ordinary meaning (*see Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed Cir. 2005) (*en banc*)), and therefore should be rejected.

A. Apotex's Proposed Construction for the Active Ingredients Is Unduly Narrow and Improperly Excludes Salt Forms

Apotex argues that the abacavir and 3TC terms[1] should be limited to their "freebase" forms and exclude salts. Specifically, Apotex appears to argue that because certain claims recite "[active ingredient] or a physiologically functional derivative thereof," and physiological functional derivate includes salts among a litany of things (Ex.1001 at 2:32-39), any claim that only recites the active ingredient excludes salts. *See, e.g.*, Pet. at 21 (referring to "Freebase formulations: (Independent claims 32 and 41)"). Such a narrow interpretation, however, is inconsistent with the '191 patent claims and specification.

The '191 patent makes clear that "[a]ll ***salts*** . . . are within the scope of the present invention." Ex.1001 at 3:19-27. Consistent with that description, claim 35 states that abacavir alone "is the succinate salt." The only way abacavir can be the succinate salt is if the active ingredient abacavir includes salts. Further, given Apotex agrees the term physiologically functional derivative is not limited to salts (Pet. at 6), Apotex does not and cannot make a claim differentiation argument for

[1] Namely, "(1S,4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol" [abacavir] and "(2R,cis)-4-amino-1-(2-hydro xymethyl -1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one" [3TC].

limiting the scope of the active ingredients. Accordingly, the term (1S,4R)-cis . . . cyclopentene-l-methanol" is broader than merely the "freebase" form and is properly construed to include salt forms of the recited compounds.

B. Apotex's Proposed Constructions for the Terms "Treatment or Prevention" and "Therapeutically Effective Amount" Are Contrary to Their Plain and Ordinary Meaning

Apotex admits that these terms should be given their ordinary meaning, but improperly argues that neither requires "any particular magnitude of effect or any particular level of efficacy." Pet. at 7. The language itself is clear: an animal must be treated with an amount of each active ingredient that is therapeutically effective. Nonetheless, whether this includes a transient, minimal effect (as Apotex contends) is irrelevant as there is no dispute that the only ***motivation*** in the field was to improve upon the prior art, not to pursue a less effective combination. *See infra* § VII; Ex.2009 (Ho Decl.) ¶ 74, 160, 167; Ex.2149 at 38:11-21; Ex.1034 at 19.

C. Apotex's Proposed Construction for "Ratios … By Weight" Is Inaccurate

Apotex recognizes this term represents a range of possible relative weights of the drugs recited in the claim, but appears to misunderstand the required relationship. Apotex's example of "1 to 2:1" actually refers to a two-drug combination, not three as Apotex contends, where the first compound is present in a relative amount of "1 to 2" times as much as the second compound. The three-

drug combination claims require ranges of ratios where the compounds, for example, "are present in a ratio of 1 to 10:1 to 10:1 to 5 by weight." This simply means that the compounds can be present in combination in relative ranges of 1 to 10 for abacavir, 1 to 10 for zidovudine, and 1 to 5 for lamivudine. The specification confirms this meaning. *See, e.g.*, Ex.1001 at 4:17-22.

VI. THE LEVEL OF ORDINARY SKILL

Apotex contends a POSA would be a person who "[t]ypically" would have a medical degree or Ph.D. in virology or a related field. Apotex offers no factual basis to support that level of skill. A person of ordinary skill ("POSA") would have had either: (a) a Ph.D. in chemistry, biochemistry, virology, or other biological sciences or equivalent experience in a relevant field (*e.g.*, a master's degree in chemistry, biochemistry, virology, or other biological sciences and two years of additional experience in a relevant field, or a bachelor's degree in one of these disciplines or a related discipline with four years of additional relevant experience); or (b) a medical degree and two years of additional experience as a resident, fellow, or the like conducting clinical or laboratory research involving antiviral agents. Ex.2009 ¶¶ 27-28. During trial in district court, ViiV's expert testified without contradiction that both sides' definitions referred to a "junior biomedical scientist" or one of comparable skill and experience." Ex.1024 (Greco) 345:7-10.

VII. APOTEX HAS FAILED TO SHOW CAMERON AND DALUGE RENDER CLAIMS 1-51 OBVIOUS UNDER GROUND 1

Apotex's case for obviousness is based on classic hindsight reasoning with the claimed invention serving as the roadmap. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1073 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933 (2013) ("retrac[ing] the inventor's steps" is "hindsight"); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."). Instead of looking at the universe of available compounds as a whole and considering their merits, Apotex starts its argument ***with the claimed combination*** of three NRTIs. *See, e.g.*, Pet. at 13-15. With no regard for the teachings in the field, Apotex then argues that a POSA would combine those three NRTIs to form a triple combination and would have reasonably expected them "to be useful for treating or preventing the symptoms or effects of an HIV infection." Pet. at 19-20.

Apotex's reliance on hindsight reconstruction is reason enough to reject its challenge of the '191 patent. *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (improper "to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.");

Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364-65 (Fed. Cir. 2008) (It is improper to "retrace[] the path of the inventor with hindsight, discount[] the number and complexity of the alternatives, and conclude[] that the invention . . . was obvious"); *see also InTouch Techs., Inc. v VGO Commc'ns., Inc.*, 751 F.3d 1327, 1348-49 (Fed. Cir. 2014); *Otsuka*, 678 F.3d at 1296.

The question is not—as Apotex assumes—whether a POSA, if presented with the claimed combinations and told to combine them against all teachings to the contrary, would have expected that they would have some effect (however fleeting). The proper question is what, if anything, would have ***motivated*** a POSA to pick the claimed combination ***in the first place***. *Cyclobenzaprine*, 676 F.3d at 1068-69 (The inquiry ***begins*** with the motivation—*i.e.*, whether a POSA "would have had reason to combine the teaching of the prior art references" in the first place.); *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010) (determining whether there was an apparent reason to combine is a factual inquiry into demands in the field, and the background knowledge of a person having ordinary skill in the art).

Further, "the expectation-of-success analysis ***must match the highly desired goal***" that motivates a POSA, not whatever degree of performance is in the claims, and not some "different goal that may be a less challenging but also less worthwhile pursuit." *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir.

2013); *see also Yamanouchi Pharm. Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000). As the district court found and Apotex's expert admitted, the goal was ***to improve upon*** the prior art, including the AZT/3TC combination. Ex.1034 at 19; Ex.2149 at 38:13-21 (researchers sought "new and better therapies" "to accomplish improved therapeutic efficacy against HIV"). In light of that goal and the teachings of the art as discussed below, a POSA would have looked to other compounds for potential combinations and, even if she had looked at the claimed combinations, would have thought they would fail. In sum, Apotex has not shown by a preponderance of the evidence that the claims of the '191 patent are unpatentable over the combination of Cameron and Daluge.

A. Neither Cameron nor Daluge Disclose the Claimed Combination, Nor Would They Be Combined

1. Cameron

The Examiner considered Cameron during the prosecution of the '191 patent before allowing the challenged claims. Ex.1001 at (56) Cited References. Cameron discloses combinations of 3TC with other agents, including AZT, protease inhibitor Ro 31-8959 (now known as Saquinavir®), and the NNRTI R-82150 (TIBO). *See, e.g.*, Ex.1002 at 3:16-35, Figs. 1, 4, 5. 3TC is described as having "synergistic antiviral effect and/or a reduction in cytotoxicity when used in combination with known inhibitors of HIV replication." *Id*. at 4:20-23. Cameron

further states that "[p]referably the inhibitor of HIV replication is selected from AZT, ddI, Ro-31-8959, or R-92150(TIBO)." *Id.* at 4:35. Aside from these compounds, Cameron does not name any other inhibitors of HIV for use in combination with 3TC, and does not disclose abacavir at all.

2. Daluge

Like Cameron, the Examiner considered Daluge during the prosecution of the '191 patent before allowing the challenged claims. Ex.1001 at (56) Cited References. Daluge states abacavir succinate "is an attractive candidate for clinical evaluation in HIV-infected patients." Ex.1003. The abstract further states that "1592U89 was equivalent in potency to AZT when tested in vitro in human peripheral blood lymphocytes against fresh clinical isolates of HIV-1 from AZT-naive patients" and that "1592U89 demonstrated synergistic activity against HIV-1 when tested in combination with AZT, ddI, or ddC." *Id*. Daluge also notes that abacavir is "activated intracellularly to (-)-carbovir triphosphate by a novel mechanism." *Id*. Daluge makes no mention of 3TC.

B. Apotex Has Not Shown a Sufficient Reason to Combine Cameron and Daluge

1. Apotex Uses Hindsight to Focus Exclusively and Incorrectly on NRTIs

Apotex's analysis mistakenly assumes a POSA would have focused only on combinations of NRTIs, and only a limited number of NRTIs at that. In reality,

HIV research was not limited or even focused on NRTIs. Rather, it focused on many different classes of anti-HIV compounds because different classes targeted different stages of the virus's life cycle. Ex.2009 ¶¶ 38-39, 56-58; Ex.1019 at 200, Fig. 1. By March 1995, a POSA understood that there were at least 10 different classes of anti-HIV compounds according to which stage of the HIV replication cycle they acted upon. Ex.2149 at 46:8-20; Ex.1019 at 200. Each of the different classes acted in different ways. For example, NRTIs and NNRTIs both targeted reverse transcription, but in different ways. Ex.2009 ¶¶ 41, 58. PIs inhibited cleavage by the protease enzyme. *Id.* ¶¶ 41, 58. Integrase inhibitors, another class, targeted the integrase enzyme. *Id.* ¶ 18.

Apotex ignores the undisputed fact that these different classes made up a vast universe of available anti-HIV compounds. But, as Apotex's expert admitted, a POSA would have considered that broad universe, including NNRTIs, PIs, and numerous others when researching and developing anti-HIV therapies. Ex.1006 ¶ 141 ("A POSA would not be limited to the NRTI class of drugs."); Ex.2149 at 53:17-55:1 (would have considered all classes including PIs and NNRTIs), 57:11-15, 206:6-17; Ex.2009 ¶¶ 38-39, 56-58; Ex.1024 (Arnold) 37:23-38:12 (would consider "every possible target in HIV"); Ex.1023 (Parniak) 205:22-206:2 ("just as interested" in NNRTIs and PIs), 207:17-208:1. In fact, by 1995, researchers had identified ***hundreds*** of compounds shown to inhibit replication *in vitro* (in the

laboratory) with dozens of such compounds already being tested *in vivo* (in humans). Ex.1019[2]; Ex.2009 ¶¶ 38-39; Ex.2149 at 55:8-11 (admitting that "[a]s of March 1995, there were hundreds of available anti-HIV compounds"); Ex.1024 (Larder) 209:18-210:20, 211:14-18; Ex.1023 (Parniak) 204:23-205:2. In fact, ***hundreds*** of NRTIs were known to have anti-HIV activity. Ex.1024 (Arnold) 37:8-11. Moreover, by this time at least ***thirty-five*** drugs were already in human clinical trials, including five NNRTIs and eight PIs. Ex.2009 ¶ 39 (Table listing the drugs, their mechanism of action, and the prior art references); Ex.2149 at 79:20-80:12, 87:17-20.

Although Apotex never identifies the significance of PIs and NNRTIs (Pet. at 10), the evidence showed that by March 1995, researchers saw more promise in PIs and NNRTIs than other classes of drugs. Ex.2009 ¶¶ 57-58; Ex.2149 at 71:12-20 (PIs were a "most promising class"),80:14-19 (PIs considered superior to NRTIs), 86:15-88:22 (NNRTIs were "a promising class" with many advantages); Ex.2032 (Biotechnology Newswatch, *Agouron Starts Clinical On Anti-HIV Drug*

[2] While Ex.1019 was published in April 1995, it is a review article that describes compounds discussed in literature before March 1995. Ex.2009 ¶ 38 n. 1. The reference therefore discloses anti-HIV compounds known before March 30, 1995. *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

(11/7/1994)) (PIs are "by far the most promising class of anti-HIV drugs presently in sight"). NNRTIs and PIs were known to be more potent than NRTIs. Ex.2149 at 72:3-6 (PIs), 80:8-12 (PIs 10 times more potent than AZT), 86:21-87:2 (NNRTIs). Both had also shown safety, good pharmacokinetics, and efficacy in humans. Ex.2009 ¶¶ 576-58; Ex.2149 at 71:22-72:2, 79:20-80:12. More PIs were in clinical development than NRTIs (Cross Tr. 80:5-7; Ex.1025 (Ho) 77:12-20), and PIs had an advantage over NRTIs and NNRTIs as only PIs could prevent already-infected cells from creating infectious HIV copies. Ex.2149 at 85:5-18; Ex.1025 (Ho) 81:23-82:13. In short, as Apotex's expert conceded, there were many promising anti-HIV agents for a POSA to consider, and no reason to focus exclusively on combination of solely NRTIs.

2. There Was No Reason to Combine Daluge with Cameron Out of the Thousands of Possible Combinations

Although Apotex treats combinations as a given as of 1995, Apotex's own expert admitted monotherapy remained a "reasonable option" as of 1996. Ex.2149 at 116-21-117:1; Ex.2009 ¶¶ 63-67. But even if a POSA considered designing a combination, Apotex fails to address the fact that abacavir was just one of hundreds of available anti-HIV agents. *See supra* § VII.B.1. As Apotex's expert conceded, "given the wealth of anti-HIV agents, the number of combinations was astronomical." Ex.2149 at 57:17-21; Ex.2009 ¶ 100 (even if only 120 agents, that

would provide more than 7,000 possible two-drug combinations and more than 280,000 possible three-drug combinations)]. Further complicating the matter, HIV research was unpredictable. Ex.2009 ¶¶ 71-73; Ex.2149 at 64:5-9.

Apotex argues as of March 1995, "combinations provided benefits over monotherapies for treating HIV infections." Pet. at 1. But, Apotex fails to acknowledge that almost all combinations failed to show any benefit over monotherapy at that time. For example, studies found that AZT/ddI failed to provide a benefit over monotherapy and that ddI monotherapy was better. Ex.2009 ¶¶ 64-66; Ex.2149 at 97:3-13; Ex.2061 (Ragni et al., *Combination Zidovudine and Dideoxyinosine in Asymptomatic HIV(+) Patients*, PROG. AND ABST. 8TH INT'L CONF. AIDS, Abst. No. MoB 0055 (1992)). Similarly, another study showed that AZT/ddC did not provide a survival benefit over AZT alone, and actually had an "***increased*** incidence of ***serious toxicity*** in patients with advanced disease." Ex.2004 (Sande, *Antiretroviral Therapy for Adult HIV-Infected Patients*, 270 J. AM. MED. ASSOC. 2583-2589 (1993) at 2587 (discussing ACTG 155); Ex.2009 ¶ 64, 66; Ex.2149 at 96:9-12 (admitting AZT/ddC had not been shown to be superior to AZT or ddC monotherapy). The results from that study "caused a great deal of disappointment in the field" and "helped to darken that period for AIDS patients." Ex.1025 (Ho) 92:20-94:6; Ex.2009 ¶ 64, 66; Ex.2065 (Hammer et al., *Issues in Combination Antiretroviral Therapy: A Review*, 7 J. ACQUIRED IMMUNE

DEFICIENCY SYNDROMES, S24-S37 (1994) at S35-36 ("no clear-cut clinical benefit has been demonstrated" for combinations, and "the reality is that patients are ***not*** flocking" to combination therapy). Thus, as of March 1995, combination therapy largely failed to show improvement over monotherapy due to drug resistance.

The only combination shown to be more effective than monotherapy in clinical trials was AZT/3TC. Ex.2009 ¶ 67; Ex.1025 (Ho) 82:18-83:4. The results of initial trials on AZT/3TC were first announced in late 1994 and early 1995, just before the '191 patent was filed. Ex.1013 at 2. This singular success was seen as a "breakthrough" (Ex.1023 (Zingman) 338:5-339:11), and a "breath of fresh air" (Ex.1013 at 2), as AZT/3TC was "the ***first and only*** combination to show such a pronounced prolonged effect." Ex.1012 at 12; Ex.1025 (Ho) 96:23-97:13; Pet. at 14 ("a POSA would have understood the 3TC/AZT drug combination taught by Cameron was one of the most effective anti-HIV treatments available").

AZT and 3TC had non-overlapping resistance profiles because each selected for different resistance mutations. In fact, the success of AZT and 3TC was attributed to a unique interaction that is the opposite of cross-resistance: 3TC rapidly selects for the mutation M184V, which while making the virus highly resistant to 3TC, actually ***reverses*** resistance to AZT and makes the virus again sensitive to AZT. Ex.2009 ¶ 68; Ex.1024 (Arnold) 12:7-17, 39:7-15; *id*. (Larder) 219:1-17, 220:11-15; Ex.1013 at 2; Ex.2055 (Tisdale et al., *Rapid In Vitro*

Selection of Human Immunodeficiency Virus Type 1 Resistant to 3'-thiacytidine Inhibitors Due to a Mutation in the YMDD Region of Reverse Transcriptase, 90 PROC. NAT'L. ACAD. SCI. USA, 5653-56 (1993) at 5655. As a result of a unique interaction with the M184V mutation strongly selected for by 3TC, AZT maintains its effectiveness for a longer period of time than it does as a monotherapy.

From that singular, unique success, Apotex attempts to argue that Cameron's generic statement that the AZT/3TC combination can be used with "other therapeutic and/or prophylactic ingredients" (Ex.1002 at 6:1-5), would motivate a person to add abacavir to AZT/3TC. But only through impermissible hindsight can one derive the claimed triple combination from Cameron's blanket statement in the face of known reasons not to try the claimed combinations, including among other things combinations of NRTIs had failed in the clinic and the availability of a multitude of more promising compounds. Ex.2009 ¶¶ 100-101; Ex.2149 at 71:12-72:6 (admitting PIs held great promise by 1995 based on excellent safety and tolerability, and greater potency over NRTIs), 79:20-80:19 (same), 94:17-95:4 (admitting POSA's awareness of failure of AZT/ddC combination).

A POSA would have understood that, far from validating ***all*** possible combination approaches, the success of AZT/3TC was a breakthrough, not easily replicated. Apotex cites nothing to suggest the unique characteristics of AZT/3TC could reasonably be extrapolated to other, untested combinations. That all but one

combination failed to show a benefit over monotherapy in the clinic underscores the lack of guidance for a POSA as well as the unpredictability in the field at that time. Ex.2009 ¶¶ 67-68; Ex.1023 (Zingman) 21:5-12 (there "were still many questions about how to best use combination therapy"); *id*. 23:21-24:5 ("It was a difficult decision to know whether or not to give them two toxic drugs or only one…").

Apotex also argues in conclusory fashion that a POSA would combine abacavir with AZT and 3TC based on the disclosure of Daluge. Pet. at 19. But, even were a POSA to contemplate a three-drug combination beginning with AZT/3TC, abacavir was not the obvious choice of compound to add. Apotex fails to explain why a POSA, to the extent she was considering a three-drug anti-HIV combination, would pick abacavir (Daluge) from the multitude of alternatives, including much more promising drugs from different classes with considerably more favorable toxicity and resistance profiles.

Further, Apotex fails to adequately explain why a POSA would have focused on Daluge. The Daluge abstract was part of a book of more than one ***thousand*** abstracts published for the October 1994 "ICAAC" conference. Ex.1003; Ex.2006 (Tisdale et al., *Anti-HIV Activity of (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89)*, Abstract No. I82, ABSTRACTS 34TH INTERSCI. CONF. ON ANTIMICROBIAL

AGENTS & CHEMOTHERAPY (Oct. 4-7, 1994)). Notably, only a few abstracts mentioned abacavir. Ex.2009 ¶¶ 43-44 Ex.1023 (Zingman) 44:20-45:17. And one of that handful, which Apotex ignores, reported that abacavir was ***50 to 100 times less potent*** than AZT. Ex.2009 ¶ 46; Ex.2149 at 158:12-159:6; Ex.2006. Further, most of the anti-HIV abstracts focused on the more promising PIs, with some references to NNRTIs. Ex.2006; Ex.2009 ¶ 44, 58; Ex.1025 (Ho) 101:19-103:9. Apotex's expert conceded he failed to discuss any of them in his declaration and, in fact, he could not recall if he had even looked at any of these abstracts. Ex.2149 at 135:16-151:12 (admitting most of the references concerned PIs and that he failed to discuss any of them in is declaration); 134:16-22. Apotex's expert's admitted reason for relying on Daluge was that Apotex's counsel gave the reference to him. Ex.2149 at 134:6-14.

Apotex also argues that a POSA would focus on abacavir because it "penetrates the central nervous system." Pet. at 19. But AZT and other compounds also shared that property. Ex.2009 ¶ 50. Given that, Apotex fails to explain why a POSA would focus on this property. Regardless, from a POSA's perspective, this property would not overcome the major concerns of cross resistance and intolerable toxicities. Ex.2009 ¶ 50; Ex.1025 (Ho) 108:6-109:2.

3. There Was No Particular Motivation to Combine Three NRTIs

Apotex fails to explain why a POSA would rely on Cameron or Daluge to pursue any three-drug combination, let alone a triple NRTI combination. Apotex must provide a sufficient rationale for why a POSA would pursue the claimed combinations. *BSP Software LLC et al. v. Motio, Inc.*, IPR2013-00307, Paper 10 at 17 (Rejecting Petitioners' conclusory rationale for combining references to arrive at the claimed invention.) Rather, Apotex appears to assume that because a single two-drug combination exhibited a degree of success, it would be obvious to a POSA to add a third drug and have a reasonable expectation of success for the resulting triple combination. Apotex's reasoning brushes aside the enormous challenges facing researchers attempting to come up with more effective, less toxic, longer-lasting anti-HIV treatments due to the tremendous unpredictability and complexity surrounding anti-HIV combination research. Ex.2009 ¶¶ 62-67, 71-73; Ex.2149 at 90:10-91:1.

Notably, Apotex fails to cite a single prior art triple-NRTI combination being tested in humans. Rather Apotex relies on a single abstract showing the testing of three NRTI's *in vitro*. Ex.1032. But the testing of three NRTIs under controlled *in vitro* conditions would not address the serious concerns regarding

toxicity and efficacy that a POSA would have with a triple NRTI combination. Ex.2009 ¶ 78.

a. Because of Toxicity, a POSA Would Not Have Combined the Claimed Three NRTIs

By March 1995, "researchers use[d] guidelines to try and select rational combinations." Ex.2149 at 59:16-20. Those guidelines included avoiding combinations with overlapping toxicities or potential cross-resistance. *Id.* at 59:21-60:1, 61:4-9. Apotex, however, largely ignores the substantial toxicity concerns that would have been prominent in a POSA's mind to the extent they contemplated any NRTI combination and in particular the claimed triple combination of abacavir with 3TC/AZT. By 1995, NRTIs were known to be toxic, particularly in combination. Ex.2009 ¶¶ 77-78; Ex.2149 at 66:17-67:15. NRTI toxicity arose in part because they inhibited normal DNA synthesis in the same way they inhibited viral replication. Ex.2009 ¶ 77; Ex.2149 at 67:19-68:1, 68:6-12, 70:6-10. NRTIs were known to have serious toxicity in humans, including anemia, renal toxicity, cardiotoxicity, and peripheral neuropathy. Ex.1022 334:9-335:13; Ex.1023 29:3-15; Ex.2149 at 66:17-67:11; Ex.2053 (Kavlick & Mitsuya, ANTI-HIV DRUG TEST SYSTEMS: SIGNIFICANCE AND LIMITATIONS, ANTI-AIDS DRUG DEVELOPMENT (Mohan & Baba, eds. (1995) at 202; Ex.2004 at 2587.

Apotex also glosses over potential toxicity concerns that surrounded abacavir itself as of March 1995. While the limited *in vitro* toxicity testing on abacavir had been generally favorable, the absence of ***human*** clinical safety data would have been discouraging to a POSA. A POSA would be aware that ddI, an NRTI like abacavir, had shown no significant toxicities until it was tested in humans and that abacavir shared the same active metabolite as carbovir, which was known to have toxic side effects that precluded its development. Ex.2009 ¶¶ 48-49; Ex.2053 at 202; Ex.1008 at 967. These issues would have raised a "major red flag" in a POSA's mind regarding abacavir's safety, especially given AZT had a "significant side-effect liability." Ex.1025 at 106:3-107:5; Ex.2009 ¶ 49; Ex.1023 (Parniak) 198:19-199:14 (carbovir toxicity relevant to abacavir); Ex.1006 ¶ 44 (quoting Coates).

Combinations of NRTIs had been shown to increase toxicities. Ex.2149 at 68:17-20 (admitting "[c]ombinations of NRTIs were known to be potentially more toxic due to overlapping toxicities"); *id.* 70:6-10 (AZT/ddC caused increased toxicities relative to AZT and ddC monotherapy); *id.* 70:12-15 ("AZT/ddI was known to increase toxicities over each agent alone"); Ex.2004 at 2586-87 (AZT/ddC); Ex.2009 ¶¶ 77-78; Ex.2003 (Barr & Torres, *Retrospective Study of Zidovudine (ZDV) or Didanosine (ddI) Monotherapy or Zalcitabine plus Zidovudine (ddC+ZDV) Combination Therapy in Patients with Early AIDS*,

ABSTRACTS OF THE 10TH INT'L CONFERENCE ON AIDS, Abst. No. PB0266 (1994)) (retrospective study showed more adverse events for combination therapy); Hammer 1994 at S36 ("a lot of issues" with combination therapy, including "potential additive toxicities").

As a result, POSAs were in general wary of combining NRTIs. Ex.2009 ¶¶ 77-78; Ex.1014 at 172 (The "temptation to combine antiviral drugs indiscriminately should be avoided in the absence of a clear rationale for using them together."). As Dr. Zingman testified in the district court, ***in March 1995***, "[i]t was a difficult decision to know whether or not to give [patients] two toxic drugs or only one…" Ex.1023 (Zingman) 23:24-24:2. Further, some NRTI combinations caused synergistic toxic side effects; one such example was the combination of AZT and carbovir. Ex.1035 at 146. Because abacavir and carbovir were known to be converted in the body to the same active metabolite (Ex.1025 106:3-17), that "synergistic toxicity" (Ex.1014 at 172), discouraged combining abacavir with 3TC and AZT. Ex.2009 ¶ 49; Ex.1023 (Laurence) 311:13-21; Ex.1025 (Ho) 140:2-141:8 (toxicity discouraged triple combination); Ex.1023 (Parniak) 183:6-13.

A POSA would also have been concerned that with three NRTIs, "we might be doing too much chain termination for normal DNA, and by and large people avoided the combination of a triple NRTI, in part for that reason." Ex.1025 (Ho)

136:20-137:5; Ex.2009 ¶¶ 77-78; *Alcon, Inc. v. Teva Pharms.USA, Inc.*, 664 F. Supp. 2d 443, 463 (D. Del. 2009) ("uncertain but probable toxicity" would discourage invention).

As Apotex's expert admitted, "[t]oxicity concerns with NRTIs spurred interest in finding and working with other classes of anti-HIV agents." Ex.2149 at at 68:13-16. In fact, as he conceded, both PIs and NNRTIs were "thought to be less toxic than NRTIs." *Id.* at 71:2-10; *see also id.* 71:22-72:2 (PIs had shown "excellent safety and tolerability"); *id.* 88:18-22 ("As of March 1995, NNRTIs were shown to have a favorable safety profile"). These toxicity concerns, including that other important classes of compounds were less toxic, would discourage a POSA from adding abacavir, an NRTI, to a double-NRTI combination.

b. The Art Encouraged Combinations of Compounds from Different Classes

Apotex cites nothing showing a motivation for a POSA to pursue a triple-NRTI combination. In fact, proponents of combination therapy regarded its potential effectiveness as more likely when ***drugs from different classes*** were combined. Ex.2009 ¶ 78. Indeed, Apotex's example of a triple combination that a POSA would look to for "guidance" is a combination that includes one NRTI and two compounds from ***other classes***. Ex.1006 ¶¶ 108-109 (discussing Johnson

(Ex.1004), saying a POSA would look to it for guidance, and saying the triple combination showed complete suppression in the lab); Ex.2149 111:8-11, 113:3-19, 115:13-19 (same); Pet. at 19 (relying on Ex.1004 as a reason why a POSA would have considered a triple combination). In addition, the Johnson reference (Ex.1004) discloses that the best approach when designing a combination is to include agents effective against both acute and chronic infections. Ex.1004 at 908. Johnson states that NRTIs are effective against acute, not chronic, infections, whereas PIs are effective against chronic infections. *Id.*; *see also* Ex.1009 at 1288-89; Ex.2149 at 85:5:86:9. In other words, Johnson, like the rest of the state of the art did not teach combining three NRTIs. *See* Cross Tr. 112:22-113:2 (admitting that Johnson did not recommend a triple NRTI combination); Ex.2009 ¶ 78.

Consistent with the teachings of the art in 1995, even years later, Apotex's expert, as part of an international panel, did not recommend triple NRTI therapy. Ex.2149 at 118:9-12, 121:1-7; 126:10-127:20; Ex.2005 at 150. Rather, to the extent he recommended triple combinations, he recommended two NRTIs and a PI. *Id*.

Notably, neither Cameron nor Daluge provide guidance or direction regarding a triple NRTI combination, let alone motivation to pursue one. Apotex's argument to the contrary relies on the following statement in Cameron:

> The invention thus further provides a pharmaceutical formulation comprising [3TC] . . . and inhibitor of HIV replication together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients.

Ex.1002 at 6:2-5; (cited in Pet. at 19). That single passage in Cameron provides neither guidance nor direction to a POSA that would limit the vast universe of other "therapeutic and/or prophylactic ingredients." Further, the use of the word "optionally" shows the use of other ingredients is unnecessary and provides no reason whatsoever to combine AZT and 3TC with any other "ingredient." There are no scientific results or other indicia of scientific reliability that would lead a POSA to a triple NRTI, let alone trump the serious toxicity and effectiveness concerns a POSA would have adding a third NRTI to AZT and 3TC. Ex.2009 ¶ 100; Ex.2149 at 69:12-70:15. Rather, for the reasons discussed above, to the extent a POSA would have read that generic "optionally" reference as a suggestion to consider a triple combination, such person would have focused on the many other classes of anti-HIV including PIs and NNRTIs.

4. Targeting Different Nucleosides Did Not Predict Success

Apotex baldly asserts that a POSA would be motivated to combine NRTIs with different natural nucleoside base analogs—which conveniently would include the combination of abacavir, 3TC, and AZT—and would have a reasonable expectation of success in doing so. Pet. at 19. Apotex cites no evidence, however,

that a POSA in 1995 would have found that approach important, or even relevant. Indeed, Apotex's expert admitted that he had no evidence to support that theory. Ex.2149 at 106:7-107:22 (conceding he had an opportunity to collect publications and yet cited no publications to support the theory about different bases).

On the contrary, the evidence shows that: **(1)** researchers did, in fact, consider combinations of NRTIs targeting the ***same*** nucleoside bases (Ex.1013 at 2 (discussing combination of 3TC (a cytosine or "C" analog) with ddC (a "C" analog))); **(2)** as discussed above, nearly all combinations of NRTIs targeting ***different*** nucleoside bases ***failed*** to demonstrate any benefit over monotherapy (e.g., AZT/ddI and AZT/ddC), and some were antagonistic. *See* Ex.2009 ¶ 67, 107; Ex.1024 (St. Clair) 136:12-22 (abacavir (a guanosine or "G" analog) and d4T (a thymidine or "T" analog) antagonistic in combination); and **(3)** AZT/3TC worked well together because of the interplay between mutations, not because the drugs targeted different bases. *See supra* § VII.B.2; Ex.2149 at 106:2-6. In short, this post-hoc theory is unsupported and without any merit whatsoever. Ex.2009 ¶ 68, 107; *see also* Ex.1034 at 32.

5. Synergism of Other Combinations Did Not Predict Success

Apotex argues that a POSA would have been motivated to add abacavir to the AZT and 3TC combination based on a supposed expectation of synergy arising from Daluge's reporting that abacavir demonstrated synergistic activity when

tested in combination with AZT, ddI, or ddC. Pet. at 19; Ex.1006 ¶¶ 37-38, 51-55, and 73-76. There is no support for such an alleged expectation. Without actually testing a combination, be it *in vitro* or *in vivo*, a POSA could not reasonably predict how it would perform. Ex.1025 (Ho) 85:4-14; *see infra* § VII.C.2. (why a POSA could not predict synergy). Each NRTI "has to be considered on its own terms as a separate agent." Ex.2051 (Yarchoan & Broder, *Correlations Between the In Vitro and In Vivo Activity of Anti-HIV Agents: Implications for Future Drug Development*, 6 J. ENZYME INHIBITION 99-111 (1992) ("Yarchoan 1992")) at 101.

Moreoever, Marty St. Clair—the named inventor who identified the activity of AZT in the 1980s, was one of the first to test the activity of abacavir, had worked extensively with 3TC, and tested hundreds of combinations—testified that she could not predict synergy. Ex.1024 (St. Clair) 99:7-9, 102:4-21, 103:1-14, 136:2-10. Further, there are "many issues that complicate [e]valuation of combination[s]," Ex.1025 (Ho) 85:4-14; Ex.2065 at S25 (listing such issues); *see also* Kavlick at 190,, tbl. 9.2 (same). The prior art taught "that in general, you cannot predict the outcome when you're measuring the effects of two things being tested together." Ex.1025 (Ho) 145:13-146:1; *see also* Ex.1024 (Greco) 310:2-9, 311:16-312:4, 348:2-16. Moreover, synergy did not predict, or even make more likely ultimate clinical success. Ex.2009 ¶ 73, 99. Finally, synergy by itself does

not trump other concerns a POSA may have with a potential combination, including toxicity and cross resistance. *See infra* §§ VII.B.3 & 6.

6. Because of Cross Resistance, the Prior Art Taught Away from Adding Abacavir to 3TC and AZT

A reference teaches away when it "discourage[s]" a POSA from following the path taken by the inventors**.** *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326-1327 (Fed. Cir. 2009). "An inference of nonobviousness is especially strong where," as here, "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." *Id*.

While Apotex attempts to downplay the importance of resistance, its expert admits "[v]iral resistance was a significant clinical issue." Ex.1006 ¶ 30. "[R]esistant viral strains would nearly always emerge eventually and result in ***death***." *Id.*; *see also* Ex.2149 at 36:15-20. "To combat viral resistance, artisans looked to combination therapies to provide more complete viral suppression." *Id.* ¶ 31. Yet, both Apotex and its expert were silent on the fact that those significant resistance concerns counseled strongly against combining compounds that were cross resistant. *See* Ex.2149 at 15:21-16:1 (admitting declaration does not discuss cross resistance "at all"). The reason for their silence is clear: when combining cross-resistant compounds, resistance to one means resistance to the other,

rendering a combination no better than monotherapy but with potentially much greater toxicity. Ex.2149 at 62:10-16 (admitting "cross-resistance could limit or eliminate the effectiveness or two or more drugs"). Thus, cross resistance defeats the point of using combinations—to make viral resistance more difficult to develop by requiring the virus to mutate in multiple ***different*** locations at the same time. Ex.1025 (Ho) 130:20-131:10; Ex.2009 ¶ 85-86. Here, it was known abacavir and 3TC have overlapping resistance profiles, indicating a high, if not ***complete*** degree of cross resistance. A POSA would have regarded this as a powerful and compelling reason to avoid the claimed combinations. Ex.2009 ¶¶ 81, 91-95.

a. Abacavir and 3TC Were Thought to be Cross Resistant

By March 1995, it was known that abacavir and 3TC select for the same ***primary*** mutation M184V. Ex.2009 ¶¶ 89-91; Ex.2149 at 205:18-206:5 (admitting it was the primary mutation known to cause resistance to both compounds); 162:18-163:3 (3TC strongly selects for M184V); Ex.1024 (Larder) 223:11-18; Ex.1034 at 41-42. It was also known that the only other known mutations selected by abacavir, L74V and K65R, conferred resistance to 3TC as well. Ex.2009 ¶¶ 89-90, 93; Ex.2006; Ex.2149 at 160:22-161:15 (admitting Ex.2006 discloses abacavir's resistance profile); Ex.1024 (Larder) 232:16-233:20. Given the same primary mutation and overlapping resistance profiles, a POSA knew that abacavir and 3TC were likely cross resistant and should be avoided. Ex.2009 ¶ 91-95;

Ex.2149 at 124:21-125:1 (admitting "cross-resistance was to be avoided"); *id.* at 62:17-63:17 (admitting that a POSA "would want to select compounds that did not select for mutations that would lead to cross-resistance").

Apotex's Petition, not surprisingly, makes ***no mention*** of cross resistance at all or that abacavir and 3TC shared overlapping resistance profiles. Yet, as Apotex's expert conceded, a POSA would consider cross resistance as a critical factor in considering potential drug combinations. Ex.2149 at 124:17-125:5 (cross resistance would have been considered because it "was to be avoided"); Ex.2009 ¶¶ 81-88; Ex.1023 (Zingman) 48:7-9 (a POSA knew to "try to avoid drug resistance").

Numerous pre-March 1995 publications specifically discouraged combinations of cross-resistant drugs. The following examples are illustrative:

- A 1993 peer-reviewed publication by Schinazi taught that (a) "[t]hree criteria should be used to select the right clinical combination," the second of which was that "the drugs ***should not be cross-resistant***." Ex.1014 at 172; Ex.1024 (Larder) 225:5-21; Ex.1025 (Ho) 113:4-13.

- A 1995 book chapter by Kavlick and Mitsuya warned that the "likelihood of cross-reactive resistance with other agents" was an "increasingly important issue" to consider. Ex.2053 at 202; Ex.1025 (Ho) 113:4-13.

- Another 1993 publication by Schinazi taught POSAs that the knowledge that 3TC (a/k/a "(-)-BCH-189") selects for the M184V mutation should

be used to monitor "for the development of resistance" and to "design rational drug combinations." Ex.2054 (Schinazi et al., *Characterization of Human Immunodeficiency Viruses Resistant to Oxathiolane-Cytosine Nucleosides*, 37 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 875-81 (1993)) at 4344; Ex.1025 (Ho) 134:22-135:23.

In short, as Dr. Ho explains in his declaration and that of HIV-resistance expert Brendan Larder in the district court litigation, the art in 1995 "strongly discouraged" a POSA from "combining abacavir and 3TC or abacavir[,] 3TC[,] and AZT because of the known cross-resistance profiles between … abacavir and 3TC." Ex.1024 (Larder) 190:12-191:1, 220:23-221:16, 232:16-233:20; Ex.2009 ¶¶ 81-95; Ex.1025 (Ho) 111:12-18, 113:4-13; 129:15-131:16. Avoiding cross resistance was one reason the art encouraged combining compounds from different as such compounds were "highly unlikely to have any problems with cross-resistance." *See supra* § VII.B.1.; Ex.1025 (Ho) 132:6-24; Ex.2009 ¶¶ 84-86; Ex.2149 at 81:15-17 ("PIs were less likely to be cross-resistant to an NRTI than other NRTIs").

b. Potency Would Not Overcome Cross-Resistance Concerns

Apotex argues that a POSA would have a reason to choose abacavir because Daluge "shows that abacavir is potent." Pet. at 19. But Apotex provides no arguments—let alone support—to suggest that a POSA would regard potency as

more important than avoiding cross resistance. In fact, as Dr. Ho explains, even a high degree of potency would not avoid or mitigate the problems associated with a cross-resistant combination. Ex.2009 ¶¶ 83-84, 94 Further, potency was not a "main criteria" for using drug combinations. Ex.1014 at 172 (identifying three main criteria: overlapping toxicities, cross-resistance, and antagonism).

Even if potency was an important factor to consider, Apotex does not and cannot explain why a POSA would have ignored cross resistance. Ex.2149 at 124:21-125:5; 125:16-126:8 (admitting cross resistance was a risk factor for drug failure to be avoided). Researchers had hundreds of available compounds, including dozens that were more advanced than abacavir. Ex.2009 ¶¶ 38-39; Ex.2149 at 55:8-11. PIs and NNRTIs had already shown a "great deal of potency in patients" and would have been a much more logical choice. Ex.1025 (Ho) 140:13-17; Ex.2009 ¶¶ 56-58. A POSA could have easily chosen a combination of potent, non-cross-resistant drugs, which is precisely what the field did with the first HAART trials. Ex.2009 ¶¶ 84-85; *see DePuy Spine*, 567 F.3d at 1326 (art supports non-obviousness if it indicates "the invention would not have worked for its intended purpose or otherwise taught away from the invention."); *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1363 (Fed. Cir. 2011) (teaching away because a POSA "would have considered about 2mM citric acid undesirable"); *Alcon*, 664 F. Supp. 2d at 463 (compound's "resistance profile" and "uncertain but probable

toxicity" both "teach away" from the invention).

Further, a POSA knew that even with a potent combination, resistance could develop. Ex.2009 ¶¶ 82-84 Ex.1024 (Larder) 234:18-235:20; Ex.1025 (Ho) 133:1-17; *see also* Ex.1023 (Laurence) 331:5-6 ("if we haven't wiped it out everywhere, we wiped it out nowhere"). Potency only goes so far. The HIV virus replicates billions of times ***per day***, generating every possible mutation of the HIV virus genome at least once a day. Ex.2009 ¶¶ 82-83; Ex.1025 (Ho) 128:16-129:14, 133:1-17; Ex.1022 (Zingman) 320:18-22. Thus, by 1995, a POSA knew that before treatment the patient would already harbor viral mutants resistant to known drugs. Ex.1024 (Larder) 211:19-213:18, 239:12-240:12, 242:22-243:11.

A POSA would also have known that no existing combination had inhibited all replication or even significantly delayed resistance in humans. Ex.2009 ¶ 69; Ex.1024 (Larder) 234:18-235:20. AZT/ddI and AZT/ddC each failed to delay resistance. Ex.1024 (Larder) 216:9-217:14. Even the most potent combination at the time, AZT/3TC ***still allowed M184V*** to rapidly emerge. Ex.2063 (Larder et al., *Antiviral Potency of AZT+3TC Combination Therapy Supports Virological Observations*, ABST. 2ND NAT'L CONF. HUMAN RETROVIRUSES, Abst. No. LB33 (1995)); Ex.1024 (Larder) 219:1-17, 234:18-235:1. Although all these facts were part of the trial record, and made part of the record in this matter, Apotex does not dispute or even address them.

* * *

In sum, the point of combination therapy was to improve on monotherapy, which eventually failed due to resistance. Ex.2009 ¶ 61, 74; Ex.1034 at 35 ("The hope in the field was that combination therapy would succeed where monotherapy failed."); *id*. at 26 ("all" NRTI monotherapies failed due to resistance);*id*. at 39; Ex.1024 (Larder) 209:11-210:3, 213:3-214:18. For the reasons discussed herein, nothing would have motivated a POSA to combine the particular compounds at issue. Moreover, what little guidance existed taught away from the claimed combinations and certainly provided no reasonable expectation of success. Ex.2009 ¶¶ 76-96; *see Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) ("no indication in the prior art which of these possible formulations would be the most promising to try."); *Institut Pasteur*, 738 F.3d at 1345 (Teaching away "counts significantly against finding a motivation to take the claimed steps with a reasonable expectation of success.").

C. Objective Indicia of Non-Obviousness Support the Validity of the '191 Patent

Apotex concedes that secondary considerations "must be taken into account." Pet. at 38. Indeed, they are one of the pillars of an obviousness analysis. *Graham*, 383 U.S. at 17-18 (1966). Here, the evidence shows that secondary considerations support the non-obviousness of the claimed combinations.

1. Commercial Success

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Commercial success supports nonobviousness if the success is linked to the merits of the claimed invention. *Id.*; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349-50 (Fed. Cir. 2012).

Apotex does not dispute that Epzicom® and Trizivir® are commercial embodiments of the '191 patent claims. Ex.1034 at 61; Ex.1025 (Ho) 166:17-167:5, 170:6-9; Ex.2009 ¶¶ 132-139. Epzicom® is a combination of abacavir/3TC. Ex.2149 at 164:2-4. Trizivir® is a combination of abacavir/3TC/AZT. *Id.* at 164:7-9.

Further, Epzicom® and Trizivir® are commercially successful and have had substantial sales. Ex.2149 at 181:3-6. Apotex does not dispute that dollar sales of of both exceeded $7 billion since launch. *Id.* at 181:3-16 (admitting Epzicom® sales exceed $4 billion and Trizivir® sales exceed $3 billion); Ex.1034 at 61 (In 2013, finding over $3 billion each). Nor does Apotex dispute that, as of the trial the number of cumulative prescriptions for each of these drugs was over 2.5 million (Ex.1034 at 61), and the cumulative U.S. profitability for both drugs was

over $3 billion (*id.*). These numbers have only increased since then.

Apotex argues that "ViiV narrowly construed the market to be limited to NRTIs," and that a "POSA would not limit the relevant market to NRTIs." Pet. at 50. While Apotex is correct that a POSA would not limit herself to NRTIs when considering agents or potential combinations (*see supra* § VII.B.1.), the market analysis is not from the perspective of a POSA and, in any event, the commercial embodiments entered the market in 2002 and 2004 (the launch years for Trizivir® and Epzicom® respectively)—many years after the '191 priority date. Further, the district court heard testimony that there are two potential relevant markets—the NRTI market or all HIV drugs. After hearing from expert economists and receiving documentary evidence, the district court found that the relevant market for a commercial success analysis is the NRTI market, not all HIV drugs. Ex.1034 at 60.

Apotex, relying solely on its expert, must simply disagree with the district court's finding in order to argue that Epzicom® and Trizivir® had "modest market share." Pet. at 50-51. But Apotex's expert admitted that he is "not an economist," and "not an expert in analyzing commercial markets or determining relevant markets." Ex.2149 at 180:9-17. In any event, even within the market for ***all*** HIV drugs, Epzicom® and Trizivir® are commercially successful as shown by sales, profits, and prescriptions. Ex.1025 (McSorley) 267:22-268:4 (Epzicom® and

Trizivir® market shares had reached 4.9% or 5% of the overall market respectively). Indeed, Apotex never disputes that over $7 billion in total sales shows commercial success. And, under cross examination, Apotex's expert admitted that Epzicom® and Trizivir® have been commercially successful. Ex.2149 at at 187:16-20.

In the face of this commercial success, Apotex resorts to arguing that there is no nexus between the success of these drugs and the claimed inventions and incorrectly asserts that "any commercial success is due to an element in the prior art." Pet. at 51. First, that mischaracterizes the prior art as there were no combinations of abacavir/3TC and abacavir/3TC/AZT in the prior art. Second, the market analysis done by ViiV's expert economist in the district court trial compared Epzicom® and Trizivir® to Combivir® (AZT and 3TC), and each drug by itself, including the purported "flat" sales. Ex.1024 (Grabowski) 357:3-359:22; Ex.1025 (Grabowski) 4:1-5:5. For the reasons stated above, the expert concluded and the district court found that in light of this analysis, the claimed combinations are commercially successful, demonstrating the requisite nexus. Ex.1034 at 63; Ex.1025 (Grabowski) 12:10-13:3; Ex.2149 at 185:3-17 (admitting commercial success even though AZT and 3TC may be sold by themselves); *see also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) (*prima facie* case of nexus when patentee shows the product is a commercial

success, and disclosed and claimed in the patent).

Indeed, Epzicom® and Trizivir® had extremely strong sales despite other subsequently discovered drugs and combinations entering the market. To the extent Apotex suggests that subsequent entries may also have been successful, that in no way detracts from the commercial success of the claimed combinations because, as Apotex's expert admitted, there may be more than one commercially successful drug in a given market. Ex.2149 at at 187:5-14; Ex.1024 (Grabowski) 365:8-19; Ex.1025 (Hausman) 40:24-41:4. In short, the commercial success of the claimed combinations supports the non-obviousness of the '191 patent claims.

2. Unexpected *In Vitro* Synergy

There is no dispute that the claimed combinations showed *in vitro* synergy. Pet. 39-40; Ex.1034 (finding combinations showed *in vitro* synergy); *see also* Ex.2146 (Daluge, S. et al. *1592U89, a Novel Carbocyclic Nucleoside Analog with Potent, Selective Anti-Human Immunodeficiency Virus Activity*, 41(5) 1082 ANTIMICROBIAL AGENTS & CHEMOTHERAPY (May 1997)) at Fig. 2 (abacavir/3TC synergistic); Ex.2009 ¶¶ 104-105, 111. Rather, Apotex argues that that synergy was not unexpected and any synergy is attributable to the prior art. *Id.* On the contrary, the evidence shows that a POSA would have found the synergy surprising. Ex.2009 ¶¶ 106-110, 112-113.

Apotex assumes that synergy for one combination equates to an expectation

of synergy for a different, untested combination. Pet. at 41-52. But each compound "has to be considered on its own terms as a separate agent." Yarchoan 1992 at 101. There was simply no way to predict how abacavir and 3TC or abacavir, AZT, and 3TC would interact in combination. Ex.2009 ¶¶ 106-107, 112-113; Ex.1024 (Greco) 311:16-312:4. The prior art taught "that in general, you cannot predict the outcome when you're measuring the effects of two things being tested together." Ex.1025 (Ho) 145:13-146:1; Ex.2009 ¶¶ 106-107, 112-113. Even Apotex's expert conceded HIV work was unpredictable and that one would have to conduct the tests in order to get the results. Ex.2149 at 64:5-13.

During prosecution of the '191 patent, inventor Ms. St. Clair submitted a declaration that supported the unexpected synergy of the triple combination. Ex.1033 at 220-243 [confirm]. Specifically, it reported *in vitro* results for the triple combination, found it "was synergistic," and commented that the synergistic effect was unexpected because the each of the drugs shares the same viral target. Apotex criticizes that last statement, trying to argue that the drugs target different nucleoside bases. Pet. at 40. But Apotex distorts the record. There is no dispute that NRTIs have the same viral target--the reverse transcriptase enzyme. Ex.2149 at at 65:2-9 (admitting all NRTIs have the same viral target). Further, Apotex's nucleoside base argument is not supported by ***any*** evidence as demonstrated by the fact that neither Apotex nor its expert cited anything to support it. *See also*

Ex.2009 ¶ 42. Regardless, the prior art shows that combining NRTIs corresponding to different base analogs did not make synergy more likely. Ex.2009 ¶ 107; Ex.1025 (Ho) 98:1-18. For instance, while anti-HIV compounds abacavir and d4T are different in natural base analogs—corresponding to Guanosine ("G") and Thymidine ("T") respectively—they were antagonistic in combination. Ex.1024 (St. Clair) 136:12-22.

Apotex argues that synergy in the claimed combinations would not be surprising in light of the closest prior art, which Apotex asserts is Cameron for claims 1-19, 21-24, and 31-47 (the three-drug claims) and Daluge for claims 20, 25-30, and 48-51 (the two-drug claims). Pet. at 41, 43. But Petitioner's argument misses the mark as neither the disclosure of synergy for AZT/3TC in Cameron, nor that of AZT/abacavir in Daluge, provide any teaching that would allow a POSA to predict synergy in the claimed combinations. Ex.2009 ¶ 109, 113. Rather, no prior art combination was predictive of what would occur with the claimed combinations. Ex.2009 ¶¶ 106-110; *e.g.*, Ex.1025 (Ho) 145:13-146:1; Ex.1024 (Greco) 310:2-9; *see also Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (the invention's results were unexpected regardless of the closest prior art). The evidence showed that, even in consideration of Apotex's alleged closest prior art, the triple combination provided an unexpected synergistic effect. *See* Ex.2009 ¶¶ 111-113 (explaining how Ex.2092, a 2002 experiment, shows the

claimed triple combination was more synergistic than fifteen other triple combinations).

3. Long Felt, Unresolved Need and Unexpected Clinical Efficacy

Attempting to argue that the claimed combinations did not satisfy a long-felt need and unexpected clinical success, Apotex argues that "any alleged need for HIV treatment was met before March 1995" by the AZT/3TC combination. Pet. at 47. The history of the AIDS crisis, and Apotex's own expert, belie that argument. After the limited clinical trial results for AZT/3TC were reported, HIV research did not come to a grinding halt. *See, e.g.*, Ex.2149 at 38:18-39:13. A POSA would have sought to improve upon the state of the art, including AZT/3TC. *Id.* 44:6-9. And, as Apotex's expert admitted, there remained a need for less toxic therapies that delayed resistance even longer. *Id.* at 44:10-15.

The claimed combinations have satisfied those needs, prolonging lives by providing safer, longer-lasting clinical efficacy. In addition to providing a sustained and potent anti-HIV effect, the claimed combinations have excellent safety profiles and low toxicity, making them well-tolerated by patients. Ex.2009 ¶¶ 160-164; Ex.1025 149:12-150:12, 153:17-154:18. Further, the combination of abacavir and 3TC is to this day only one of two recommended initial NRTI backbones. Ex.2149 at 176:12-177:21, 178:17-179:7 (referring to Ex.2008). And

the claimed triple combination was the only FDA-approved triple NRTI to ever be approved. Ex.2009 ¶ 121.

Apotex's argument that the claimed combinations have not shown "unexpectedly superior results" over the prior art is incorrect. Pet. at 44. In fact, both the claimed double and triple combinations surpassed AZT/3TC. Ex.1034 at 50; Ex.2009 ¶¶ 123-127 (explaining how Exhibits 2098 (Rozenbaum), 2099 (Ait-Khaled), 2100 (Staszewski), and 2101 (Vibhagool) demonstrate clinical success of the triple); *id*. ¶¶ 116-119 (explaining how Exhibits 2094 (PENTA), 2007 (Green), and 1020 (DeJesus) demonstrate clinical success of the double)]; Ex.2149 at 174:21-175:8 (admitting Ex.2007 shows claimed combination of abacavir/3TC is more effective than AZT/3TC or AZT/abacavir). For example, abacavir/3TC was shown to be ***superior*** to AZT/3TC. Ex.2007; Ex.2149 at 175:2-8 (agreeing that Ex.2007 shows that abacavir/3TC was shown to be "more effective than AZT/3TC or AZT/abacavir"); Ex.2009 ¶ 116. Although one study found the combination to be non-inferior to AZT/3TC, that was still a superior result compared to what was expected in light of the substantially disappointing results reported for other anti-HIV combinations and the apparent cross resistance of 3TC and abacavir. Further, as described above, a POSA would not have expected abacavir and 3TC to be better than or even non-inferior to AZT/3TC because the efficacy of AZT/3TC was due to the unique effect of the M184V mutation's resensitization of the virus to

AZT. For these reasons, a POSA would have thought abacavir/3TC would be a failure and thus far less effective than the combination of AZT/3TC. Ex.2009 ¶¶ 118-119.

Moreover, although Apotex attempts to downplay the clinical results of the triple combination, a POSA would not have expected the triple combination to be as good as PI or NNRTI containing regimens. *See* Ex.1033 (discussing abstracts of research done after 1995, showing that the claimed triple NRTI combination surprisingly provided results equivalent to triple combinations that combined drugs from other classes, including the PI indinavir); Pet. at 45 (referencing same without identifying the compounds from other classes). Apotex selectively quotes from a 2001 publication to suggest that the claimed triple combination was "expected" to be as good as AZT/3TC. Pet. at 45. That paper actually says that in patients who had already received AZT with or without 3TC, addition of abacavir provided only a modest response. Ex.1021 at 8; Ex.2009 ¶ 128. What Apotex, not surprisingly, does not quote is the author's observation that "the proportion of participants who maintained HIV-1 RNA levels <10 000 copies/mL for 48 weeks or more was significantly better in the [abacavir]/3TC/[AZT] group compared with the 3TC/[AZT] group." Ex.1021 at 1. That observation is consistent with the author's conclusion that the combination provided "increased antiviral activity" over the combination of AZT/3TC. *Id*. at 10.

4. Industry Praise

Industry praise for the claimed invention supports nonobviousness. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1351 (Fed. Cir. 2012); *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1352 (Fed. Cir. 2010). Both combinations have garnered industry praise for their efficacy and durability. Ex.2009 ¶¶ 146-159; Ex.1022 (Blick) 103:23-109:11 (from physicians); Ex.1024 (Grabowski) 359:23-361:16 (physicians prescribed often); Ex.1025 (Ho) 154:19-155:7 (chose Trizivir® to launch HAART in China); *id.* 157:24-158:6 (recommended by treatment guidelines). Treatment guidelines provide "high recognition from a group of opinion leaders involved in treating HIV infection." Ex.1025 (Ho) 161:5-19; *see also* Ex.2149 at 175:19-177:21; Ex.2009 ¶¶ 153-154. Notably, the single combined formulation of abacavir/3TC, marketed as Epzicom®, is currently a preferred regimen, *i.e.*, a first choice, in four out of six guidelines: the International Antiviral Society (PTX 467, 633), National Institutes of Health ("NIH")—Pediatric (PTX 637), PENTA, and European AIDS Clinical Society (PTX 636). Ex.2009 ¶¶ 147-152. Similarly, the NIH and WHO recommended the triple combination as an alternative regimen for many years. Ex.1025 (Ho) 1316:22-1317:10; Ex.2135 (ViiV_EZTZ_0010045-10209 (WHO, *Scaling Up Antiretroviral Therapy in Resource-Limited Settings* (2002))) at 10060, 10075; Ex.2129 (ViiV_EZTZ_0006377-501 (NIH Adult

Guidelines (Nov. 10, 2003))) at 6433; Ex.2134 (ViiV_EZTZ_008387-482 (NIH Pediatric Guidelines (Nov. 3, 2005))) at 8436. It was the only triple NRTI combination recommended by the guidelines. Ex.1025 (Ho) 162:22-163:10.

Apotex misguidedly argues, with no support, that industry recognition requires researchers or competitors to find the claimed combinations to be superior to other known anti-HIV therapies. In any event, as discussed above in unexpected results, researchers have conducted clinical studies and reported that the claimed combinations are surprisingly superior to or, in some cases, non-inferior to combinations thought to be better. *See supra* § VII.C.3. Second, the recommendations and guidelines referenced herein concern the collective opinion of experts in the field and are intended to provide guidance on how to treat actual patients based on clinical results concerning efficacy and tolerability for all known drug therapies. Ex.2149 at 175:19-176:11. Thus, the evidence of industry recognition far exceeds "journal articles referencing efficacy" (Pet. at 52), and supports nonobviousness.

5. Skepticism of Others

Skepticism is objective evidence that the claimed inventions were not obvious to a person of skill in the art. *Transocean*, 699 F.3d at 1352; *Envtl. Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697-98 (Fed. Cir. 1983) (disbelief by experts). Evidence of skepticism need not precede filing. *Knoll*

Pharm. Co., Inc. v. Teva Pharms. USA, Inc., 367 F.3d at 1381, 1385 (Fed. Cir. 2004) (post-filing evidence supports non-obviousness); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, No. 09-MD-2118-SLR, 2010 WL 3766530, at *2 (D. Del. Sept. 21, 2010) ("post-invention skepticism can be evidence of non-obviousness"). Two undisputed instances of skepticism from experts support nonobviousness here. *First*, after the claimed combinations had been discovered, Dr. Tisdale, a work colleague of the inventors familiar with HIV resistance, warned that abacavir and 3TC "clearly show some cross-resistance" and "***stress[ed]*** that the cros-resistance [sic] profile is a ***problem with this combination***." Ex.1025 (Ho) 163:11-24. *Second*, in 2002, a ten-author committee stated that before conducting clinical trials with abacavir and 3TC, they were "concerned that the combination … might not provide a potent or sustainable reduction in concentrations of HIV-1 RNA in plasma, since both drugs were associated with development of the M184V mutation." Ex.2004 at 738-39. This skepticism, which a POSA would have had in 1995, further demonstrates non-obviousness. Ex.2009 ¶¶ 141-143.

Apotex tries to sweep this skepticism under the rug. But, because cross resistance was a critical factor when dealing with combinations, a POSA would view Dr. Tisdale's concerns to reflect the serious reservations the research community as a whole would hold—rather than by "a single co-worker" as Apotex

contends—about the ability of a potential combination to provide the durable and effective ant-HIV efficacy needed at the time. Ex.2009 ¶¶ 141-143; Ex.2149 at 124:10-126:8.

Apotex argues incorrectly that this skepticism has no nexus to the claimed invention. But that is simply wrong—the skepticism of the committee in 2002 express;yconcerned the claimed combination abacavir and 3TC. Further, their skepticism was directly related to the ability of the combination to provide sufficient treatment or prevent symptoms or effects of HIV. Specifically, to the extent the claimed combination failed to provide a "potent or sustainable reduction of HIV-1 RNA in plasma," a POSA would regard it as failing to provide a viable treatment for HIV infection. Ex.2009 ¶ 144.

D. The '191 Patent Claims Are Not Obvious

Independent claims 1, 16, 20, 31, 32, 41, and 48 were not obvious for the reasons described above, including: as of March 30, 1995, combination therapy had generally not been shown to provide the benefits that many had hoped for; the effect of AZT plus 3TC was surprising and unexpected, but could not be extrapolated to predict success for other combinations because it depended on a unique resensitization effect; *in vitro* combination work was unpredictable, required actual testing of the combination, and was not predictive of clinical success; researchers faced hundreds of compounds from many different classes,

including classes considered more promising than NRTIs; cross-resistance and toxicity concerns taught away from combining abacavir with AZT and 3TC. And objective indicia, including commercial success, unexpected synergy and clinical efficacy, long-felt need and the failure of others, industry praise, and skepticism of others, further buttresses non-obviousness. Accordingly, dependent claims 2-5, 8, 10-11, 13-15, 17-18, 20-21, 23-27, 29-30, 33-34, 36, 38, 43-44, 46-48, 50, 51 were not obvious as they rely on non-obvious independent claims.

Further, dependent claim 4's claimed weight ratio of abacavir to AZT to 3TC in the range of 1 to 3:1 to 3:1 to 2 was also not obvious. A POSA understood that the optimum ratios for the triple combination were unpredictable and required actual testing. Abacavir had only just entered phase I clinical trials and Apotex fails to cite any evidence that taught a POSA how the drug would perform in humans or interact with AZT and 3TC. The prior art disclosed a wide range of possible doses of abacavir, AZT, and 3TC as ***individual*** agents that many of which, even when combined, fall outside claim 4's ranges. A POSA could not predict what doses of abacavir, AZT, or 3TC to use in a combination. Ex.2009 ¶¶ 171-172.

Use of abacavir, AZT, and 3TC as a single combined formulation (claims 10, 23, 29, 38) was also not obvious. The active metabolites of abacavir and 3TC had significantly differently intracellular half-lives. Ex.2009 ¶ 174, 177

(approximately 10 hour difference). A POSA would have doubted that abacavir could or should be put into one formulation with 3TC as they would have expected abacavir would need to be dosed on a different schedule. Trying to compensate for this difference by using more of abacavir, or changing the dosing schedule of the two drugs, would either increase toxicity or lower efficacy. Ex.2009 ¶ 174. A POSA would neither pursue nor reasonably expect success in combining all three drugs into a single combined formulation.

VIII. CONCLUSION

For the foregoing reasons, the Board should reject Ground 1 of Apotex's Petition and uphold the patentability of claims 1-51 of the '191 patent.

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INDEX OF EXHIBITS

Exhibit No.	Description
2001	Katzenstein Deposition Exhibit 2001 (Cimons & Maugh, *New Strategies Fuel Optimism in AIDS Fight*, L.A. Times (Feb. 20, 1995))
2002	Katzenstein Deposition Exhibit 2002 (San Francisco Examiner, *New Drug Seen as Potent HIV Fighter - 10 Times Stronger Than AZT, but Viral Resistance Perplexing* (Feb. 1, 1995))
2003	Katzenstein Deposition Exhibit 2003 (Barr & Torres, *Retrospective Study of Zidovudine (ZDV) or Didanosine (ddI) Monotherapy or Zalcitabine plus Zidovudine (ddC+ZDV) Combination Therapy in Patients with Early AIDS*, Abstracts of the 10th Int'l Conference on AIDS, Abst. No. PB0266 (1994))
2004	Katzenstein Deposition Exhibit 2004 (Sande, *Antiretroviral Therapy for Adult HIV-Infected Patients,* 270 J. Am. Med. Assoc. 2583-2589 (1993))
2005	Katzenstein Deposition Exhibit 2005 (Carpenter, *Antiretroviral Therapy for HIV Infection in 1996*, 276 J. Am. Med. Assoc. 146-154 (1996))
2006	Katzenstein Deposition Exhibit 2006 (Tisdale et al., *Anti-HIV Activity of (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89), Abstract No. I82*, ABSTRACTS 34TH Intersci. Conf. on Antimicrobial Agents & Chemotherapy (Oct. 4-7, 1994))
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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Patent Owners' Response, along with all exhibits in support, was served on March 23, 2015, by e-mail and ftp directed to counsel of record for the Petitioner as follows:

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